Audit on "Assessment of Adequacy of postoperative analgesia in a tertiary care centre;

An Observational Study.

A Dissertation submitted in partial fulfillment of M.D. Branch X (Anaesthesiology) Degree Examination of The TAMIL NADU DR.M.G.R. MEDICAL UNIVERSITY , CHENNAI, to be held in April 2013.

CERTIFICATE

This is to certify that the dissertation entitled 'Assessment of adequacy of postoperative analgesia in a tertiary care centre – An Audit"; An Observational Study: is the bonafide original work of Dr. Anity Singh Dhanyee., towards the M.D. Branch-X (Anaesthesiology) Degree Examination of the Tamil Nadu Dr.M.G.R University, Chennai, to be held in April 2013.

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A. 14 Definition of Pain

'An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.'

adopted from IASP 1979,(3)

Pain as the 5th vital sign, has been proposed by the Joint Commission on Accreditation Of Healthcare Organizations (JCAHO).(4)

B. History of Pain

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ACKNOWLEDGEMENTS

I would like to take this opportunity to offer a solemn prayer, and express my deepest gratitude towards the lord , for all the blessings bestowed upon me.

I would like to remember my parents here and thank them for their everlasting unconditional love and support in all my endeavours.

I would like to mention my institute ‘ Christian Medical College – Vellore ‘ and express my obedient respect and gratitude for all my Training.

I thank my guide Dr. Mary Korula (Professor and Head of Department of Anaesthesiology) for initiating me into this study, and for her constant support , approachability and an ever open mind to new modalities of research.

Iam very grateful to Dr. B. Antonisamy (PhD), for his patient guidance with statistical analysis.

Finally, I thank all the concerned nurses and my patients for their kind co-operation.

TITLE OF THE ABSTRACT: "Assessment of adequacy of postoperative analgesia in a tertiary care centre – An Audit".

DEPARTMENT: Anaesthesiology

NAME OF THE CANDIDATE: Dr.Anity Singh Dhanyee

DEGREE AND SUBJECT: MD Anaesthesia

NAME OF THE GUIDE: Dr.Mary Korula; Professor and Head of Department of Anaesthesiology.

PRIMARY OBJECTIVE: Assessment of adequacy of current analgesic protocols.

SECONDARY AIMS: a)Assessing the need of a pain nurse in our setting.

b) To establish the necessity of a functioning Acute pain service in Obstetrics-Gynecology department.

METHODS:

CLINICAL METHODS:

This observational study includes all Gynecology inpatients undergoing any open abdominal procedure ,with normal mental health and hospitalized for atleast 48hrs postoperatively.Our exclusion criteria includes all patients transferred directly to an intensive care unit,those who had emergency procedure or discharged in less than 48hrs. Our tool is the Comprehensive Pain Assessment and monitoring sheet/ Universal Pain Assessment Tool.During the preoperative visit patients will be made familiar with this tool.Postoperatively the first scoring will be done by the nurse,who will be educated beforehand about the study.It will be continued on the Gynecology wards by the nurses every 4 hours for the next 48 hrs. The patient will need to be reassessed 45 min later after any rescue medication also.We will be comparing the scoring done for the patient as against the analgesia been prescribed.Family members will be involved when appropriate.

STATISTICAL METHODS:

My study sample size was calculated by this formula:

Estimation of Single Proportion
Formula

$$n = \frac{Z^2_{1-\alpha/2}\, p(1-p)}{d^2}$$

Where,

p : Expected proportion

d : Absolute precision

1- α/2 : Desired Confidence level

Reference

Lemeshow S, Hosmer DW, Klar J, Lwanga SK. Adequacy of Sample Size in Health Studies. John Wiley and Sons, 1990

The results are based on calculating and tabulating frequency tables.

RESULTS:

This Audit was done on all female patients from the age group of 16 to 60 years of age.Their categorization into ASA grades was, about 50.5% of ASA grade I, 47% of ASA grade II, and 2.5% were of ASA grade III.About 39% patients underwent Total Abdominal Hysterectony.The type of Anaesthesia mostly used was spinal anaesthesia, in 43% patients.The commonly performed surgeries seemed to be Total Abdominal Hysterectomy, Vaginal Hysterectomy, Lap-assisted Vaginal Hysterectomy, and Staging Laparotomy.

Among our patients, Co-morbidities like Diabetes, Hypertension, hypothyroidism, and Obesity seemed more prevalent.After analyzing the pain scores, we found that about 67% patients were in significant pain on the first postoperative Day, and 45% on the second postoperative Day.

A review of their prescriptions was done and Tramadol based analgesic protocol was found in 49% doctor order sheets, on first postoperative day and 63% on second postoperative day.These were mostly administered by intramuscular route.Morhine based treatment was received by 42% patients on the first postoperative day and 41% on second postoperarive day.The commonly followed route for Morphine was subcutaneous.Only 15-16% patients had received the benefit of an Epidural.The Epidural infusion was continued for a maximum of 48hrs and discontinued.This infusion was being stopped whenever the patient was ambulant.Any complication like hypotension was supposed to be due to Epidural infusion. Some feedback from the nurses suggested that, they did not get adequate support from our existing personnel involved with pain services.

Dosifuser usuage was done in only 2% patients.One such infusion was discontinued due to lack of knowledge about the modality.All the protocols followed were based on a Multimodal approach, but the dosages were inadequate and frequency of administration variable.Several combination of paracetamol, voveran, proxyvon, ketonov with emeset, phenergan, ranitidine ans pantoprazole were noticed.The brand of paracetamol frequently used was Febrinil.

The most common side-effect was constipation, followed by nausea.

Ambulation was started on Day II.

This concludes the results.

AIM

Assessment of Adequacy of current Analgesic Protocols in inpatients, undergoing any open abdominal or major Gynecological operation.

OBJECTIVES

PRIMARY OBJECTIVE: Assessment of adequacy of current analgesic Protocols.

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INTRODUCTION

The review of Literature will be presented under the following headings;

A. Definition of Pain

B. History of Pain

C. Nocicepton & Types of Pain

D. Terminologies associated with pain

E. Theories of Pain

F. Epidemiology of Pain

G. Receptors of Pain

- Types of Nociceptors
- Nocineurons
- Factors activating Nociceptors

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- Central Modulation
- Neurochemical Mediators

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- Archispinothalamic Tract

K. Endogenous Pain Suppression Pathway

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M. Pain Assessment Scales

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- 0-10 Numeric Pian Rating Scale
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- Behavorial Rating Scale
- Functional Activity Score
- Visual Analog Scale
- Universal Pain Assessment Tool

N. Preemptive analgesia

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- Central Hyperexcitability

O. Influence of Anaesthesia on Stress response

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- Regional Anaesthesia

P. Analgesic Ladders

- WHO (World Health Organization) Ladder
- Modified WHO Ladder
- WFSA (World Federation of Societies of Anaesthesiologists) Ladder

Q. Multimodal Analgesia

R. Acute Pain Services

S. Pharmacology (Relevant to this study)

T. Non-Pharmacological Techniques of Pain Management

U. Practice Guidelines for Acute Pain Management in the Perioperative Setting (Updated report by the American Society of Anaesthesiologists Task Force on Acute Pain Management; published on October 20,2011)(1)

V. A Brief Note on Chronic Pain

"I don't accept the maxim 'there's no gain without pain', physical or emotional. I believe it is possible to develop and grow with joy rather than grief. However, when the pain comes my way, I try to get the most growth out of it."

~ Alexa McLaughlin.(2)

A. Definition of Pain

'An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.'

adopted from IASP 1979;(3)

Pain as the 5th vital sign, has been proposed by the Joint Commission on Accreditation Of Healthcare Organizations (JCAHO).(4)

B. History of Pain

Figure(1); Descartes' pain pathway: "Particles of heat" (A) activate a spot of skin (B) attached by a fine thread (cc) to a valve in the brain (de) where this activity opens the valve, allowing the animal spirits to flow from a cavity (F) into the muscles causing them to flinch from the stimulus, turn the head and eyes toward the affected body part, and move the hand and turn the body protectively.

Illustration as depicted in Rene' Descartes ' Traite de l'homme (Treatise of Man)1664.

The proposition of a link between peripheral sensation and the brain was put forth as early as the 17th century ,by Rene Descartes .His cartesian model(5) of a hard – wired system suggested that pain is transmitted by very fixed pathways .

The current concept of nociceptive pain follows from the ideas of R.Melzack and P.Wall in the 1960s.C.Woolf and M.Salter enumerated the principle of "pain memory" to explain chronic pain.The history of pain revolves around various lives from the immemorial past, whose subjective experiences with pain defined their very being.I would hereby like to quote a few .

The eminent novelist Frances Burney ,in 1812, underwent a mastectomy in her drawing room without any anaesthetic.She has described her agony in letters to her sister as "the most torturing pain" , She goes on to say' I needed no injunctions not to restrain my cries.I began a scream that lasted intermittently during the whole time of the incident, & I almost marvel that it rings not in my ears still.(6)"

According to the European Pain Network, people with chronic pain suffer an average of seven years.

The word pain is derived from the greek word Poine, goddess of revenge.According to greek mythology Poine was sent to punish mortal fools who had angered the gods.

The excavations in Incan archaeological sites in South America have unearthed hundreds of skulls with small holes in them.This practice called trepanation was followed by many ancient physicians apparently 'to let the pain out'.

The greek physician ,father of medicine, Hippocrates prescribed willow leaves to women in childbirth. Willow trees belong to genus salix, containing the active ingriedient of aspirin which is salicylic acid.

In ancient Egypt electric eels were fished out of the nile ,and were laid over the wounds o relieve pain. This practice is not very different from the modern day modality of TENS; Transcutaneous electrical nerve stimulation.(7)

These interesting accounts also reflect one essential aspect of the past, that the patient was and should be treated as a whole. Pain encompasses not only the physical component but also emotional, psychological, psychosocial and of course economic condition of the patient (8), and affects the whole medical infrastructure.

C. <u>Nociception & Types of pain</u>

Nociception means noci (latin for harm or injury),is the neural response to noxious stimuli. The entity of nociception is not a hard-wired process as depicted by the 17th century scientist and philosopher; Descartes.It involves elements of neuroplasticity that are dynamic with multiple points of modulation.The continuing noxious stimuli can lead to sensitization of neurons, converting acute pain to chronic.

Nociception involves :(9)

1. Transduction – Any injury causes tissue damage and release of mediators of noxious input,like prostaglandins, serotonin, substance P, bradykinin and histamine.All these inflammatory mediators generate an action potential which is called transduction.

2.Transmission – This is the conveying of above generated action potential to spinal cord and higher centres.

3.Modulation – This phase involves inhibiting painful stimulus, by an endogenous descending inhibitory pathway.

4.Perception – When pain is consciously perceived by the individual.

Postoperative pain can be divided into acute and chronic pain.(10)

Acute pain – It is primarily nociceptive and perceived immediately after surgery upto a week.

Chronic pain – This involves nociceptive, neuropathic, psychological and behavorial factors. It is referred as chronic, if persisting beyond 3 - 6 months of the insult.

Acute pain is differentiated further into somatic and visceral pain.

Salient features:

Somatic pain is divided into superficial and deep pain;

a.Superficial pain – nociceptive input signals arise from skin, subcutaneous and mucous membranes.It is a well localized, sharp, pricking and throbbing sensation.

b.Deep pain - The locus for deep pain are the muscles, tendons, joints and bones.It is less well-localized with a dull aching quality and is influenced by the stimulus intensity and duration.

Visceral pain;

Arises from an internal organ or its covering .

Subtypes- a) true localized visceral and parietal

b) referred visceral pain and parietal

Visceral pain is dull ,diffuse, in the midline and associated with autonomic lability, in the form of nausea,vomiting ,diaphoresis or shock.

In contrast to this Parietal pain is of a sharp ,stabbing nature.it involves the area around the organ or is referred from a distant site owing to our embryological dermatomal distribution; as listed in Table(1).

Table(1);Cutaneous dermatomal distribution(10)

Site	Dermatome
Central diaphragm	C4
Lungs	T2-T6
Heart	T1-T4
Aorta	T1-L2
Esophagus	T3-T8
Pancreas and spleen	T5-T10
Stomach,liver and gall bladder	T6-T9
Adrenals	T8-L1
Small intestine	T9-T11
Colon	T10-L1
Kidney, ovaries and testes	T10-L1
Ureters	T10-T12
Uterus	T11-L2
Bladder and prostate	S2-S4
Urethra and rectum	S2-S4

Our ability to perceive various modalities of sensations are arbitrarily grouped under two classes. These are the Epicritic/nonnoxious and Protopathic/noxious sensations.

Table(2); Modalities of sensations(10)

Sensation	Modalities	Receptor types	Category of nerve fibres
Epicritic	Lighttouch,pressure,proprioception,temperature discrimination	Low-threshold receptors	Large myelinated nerve fibres
Protopathic	Pain	High threshold receptors	Smaller, lightly myelinated (Aδ) and unmyelinated C-type nerve fibres

Physiological pain

It forms part of the defence network of the body .There is activatin of High-threshold sensory nerve fibres, by a minimal stimuli that causes no tissue damage.It warns the subject to move away from the source of such input.

Pathological pain

The presence of intense and prolonged noxious stimuli leads to tissue damage.Such injury increases the sensitivity of nerve fibres, due to low threshold or hyperalgesia.and causes pain both at the site; primary hyperalgesia and secondary hyperalgesia, when it sensitizes the dormant sensory neurons also.

Neuroplasticity

The pain transmission pathway from periphery to the higher centres gets sensitizsed by any noxious input.This response gets heightened by injury.The Aδ and C fibres get activated and intercept next higher order neurons.The release of neurokinins and glutamate nerotransmitters sensitizes dorsal horn cells.There is expansion of the receptive field.There is an increase in the activity of NMDA receptor, during this process.

Neuropathic pain(11)(12)

The International Association for the Study of Pain (IASP), has defined neuropathic pain as pain, resulting from disease or damage followed by the dysfunction of the peripheral and central nervous system.

This category of pain is found to be difficult to diagnose and treat compared to other etiologies of pain.The plasticity of the nervous system gets modified; central as well as peripheral.

The hallmark is painful sensation arising from an area with altered sensation like numbness or hyperexcitability.Patients complain of shooting type of pain, radiating or stabbing in character.Even cold breeze or clothes brushing against the sensitive area is painful.

Assessment is done by using clinical examination and bed-side tests(11) like Leeds Assessment of Neuropathic Symptoms and Signs; LANSS pain scale or the pain DETECT questionnaire.These are evidenced to have 80% accuracy.

Such patients have poor physical and mental health, following the poor quality of life that develops.The management of neuropathic pain puts a lot of burden on the economic infrastructure of any centre, since it is different from the standard modalities of care.

A classification of Neuropathic pain followed in general is as follows:

Classification of neuropathic pain and associated syndromes

Neuropathic pain is divided into four categories:

1.The lesions involving the peripheral nervous syste:

a) Neuralgias like trigeminal neuralgia, glossopharyngeal neuralgia, post-traumatic neuralgia, and post-herpetic neuralgia.

b) Nerve entrapment syndromes

c)Ischaemic neuropathy

d)Nerve involvement following malignancy or radiation

e) Phantom limb pain

2.Polyneuropathies

a)Metabolic and Nutritional like Diabetes Mellitus, pellagra, beriberi, amyloidosis, hypothyroidism.

b) Toxicity following Alcohol consumption, isoniazid, antiretroviral medicines, chemotherapy.

c) Infective and Autoimmune causes like Guillian-Barre syndrome, HIV.

d) Malignancy

e) Hereditary like Fabry's syndrome

3.Central nervous system lesions

a) Spinal cord injury

b)multiple sclerosis

c)stroke

d)Parkinson's disease

4.Complex neuropathies

a) Complex regional pain syndromes I and II

Table(3); Treatment recommendations for peripheral neuropathic pain adapted from recent guidelines and algorithms(11)

Medication class/drug	Recommended stage of treatment	Dose range (mg/day) for maintenance	Combined NNH for study withdrawal (range)	Combined NNT for 50% pain relief (range)
Antidepressants				
Tricyclics (nortriptyline, desipramine, amitriptyline, imipramine)	First	25-150; secondary amine tricyclic antidepressants are in favour (nortriptyline, desipramine)	14.7 (10.2-25.2)	2.1/2.5/3.1 (1/8-3.7)
Duloxetine	First or second	60-120	Relative risk not significant	4.1/5.2 (2.9-8.5)
Venlafaxine	First or second	150-225	Relative risk not significant	4.6 (2.9-10.6)
Paroxetine, citalopram, bupropion	Third		Relative risk not significant	6.8 (3.4-441)
Anticonvulsants				
Pregabalin	First	150-600	11.7 (8.3-19.9)	4.2/4.9 (3.7-7.6)
Gabapentin	First	1200-3600	17.8 (12-30)	4/4,4 (3.3-6.1)
Carbamazepine	First (only for trigeminal neuralgia)	200-1200	21.7 (12.6-78.5)	2.0 (1.3-2.2)

Medication class/drug	Recommended stage of treatment	Dose range (mg/day) for maintenance	Combined NNH for study withdrawal (range)	Combined NNT for 50% pain relief (range)
Lamotrigine	Second or third	200-400 (slow titration)	Relative risk not significant	4.9 (3.5-8.1)
Oxcarbazepine	Second (only for trigeminal neuralgia)	600-1800 (fewer safety concerns)	Relative risk not significant	NA
Topiramate	Third	200-400	6.3 (5-8)	7.4 (4.3-28)
Valproate	Third	1000	Relative risk not significant	2.8 (2.1-4.2)
Opioids*				
Oxycodone	Second or third	10-120	Relative risk not significant	2.6 (1.9-4.1)
Morphine	Second or third	15-300	Relative risk not significant	2.5 (1.9-3.4)
Tramadol	Second or third	200-400	9 (6.0-17.5)	3.9/4.8 (2.6-26.9)
Methadone	Second or third	15	NA	NA
Miscellaneous				
Topical lidocaine (patch 5%; gel)	First or second (only for localised areas of pain, focal neuropathy, allodynia)	1-3 patches/day applied for 12 h	Relative risk not significant	4.4 (2.5-17.5)
Cannabinoids	Third	5-15	Relative risk not significant	9.5 (4.1-∞)
Topical capsaicin	Third		11.5 (8.1-19.8)	6.7 (4.6-12)

- NNH=number needed to harm on the basis of withdrawal from neuropathic pain studies owing to adverse effects.
- NNT=number needed to treat on the basis of 50% pain relief from baseline.
- *The combined NNH for study withdrawal (range) for opioids overall = 17.1 (10-66).

An epidemiological survey suggests 6-8% population reporting pain of neuropathic character.

A recent study(11) has tried to explain the mechanism involved in neuropathic pain. After any injury to a peripheral nerve, the noxious heat gated VR-1 receptor gets over expressed.This receptor is located normally only on the C fibres cell bodies.This receptor is activated on the uninjured Aδ fibres, on the dorsal horn cells.So it appears that uninjured neurons contribute to this pain generation as well.

D. <u>Terminologies associated with pain</u>:(10)

Allodynia- When an ordinary nonnoxious stimulus is perceived as pain.

Analgesia- When there is no perception of pain.

Anaesthesia- Alleviation of all sensations.

Anaesthesia dolorosa- When pain is perceived in an area lacking all sensation.

Dysesthesia- An abnormally unpleasant sensation with or without any stimulus.

Hypalgesia/hypoalgesia- When there is diminished response to noxious stimulus.

Hyperalgesia- There is heightened response to noxious stimulus.

Hyperesthesia- When a mild stimulus elicits an increased response.

Hyperpathia- This is when hyperesthesia, allodynia and hyperalgesia coexist, and are associated with overreaction and post - stimulus persistence of the sensation.

Hypesthesia/hypoesthesia- Reduced cutaneous sensation to modalities like light touch, pressure or temperature.

Neuralgia- Pain along the distribution of nerves.

Paresthesia- Perception of abnormal sensation with apparently no stimulus.

Radiculopathy- When the nerve roots are functionally abnormal.

McCaffery (cited in Adams and Bromley, P192,1998) states the experience of pain as being “what the experiencing person says it is, existing when he says it does.” Pain is conceived and experienced in a very subjective individualized manner.

E. Theories of pain(13)(14)

Specificity theory:

This theory is based on Muller’s law of ‘specific nerve energies’ which states that, any stimulus applied to a receptor would produce similar sensation in the brain, regardless of the stimulus.Specificity theory conceives of a separate pain system with its own distinct receptors, nerve fibres, pathways to the brain and a specific area in the brain to process pain. This concept was further expanded by Von Frey.

Pattern theory (Intensity theory):

This theory as proposed by Goldschneider in 1896, states that the pattern of stimulation of nerve endings pertaining to its frequency and intensity, when applied to normal sensations like touch, temperature or pressure would be interpreted as pain .This happens only with intense stimulation.

Gate control theory:(15)

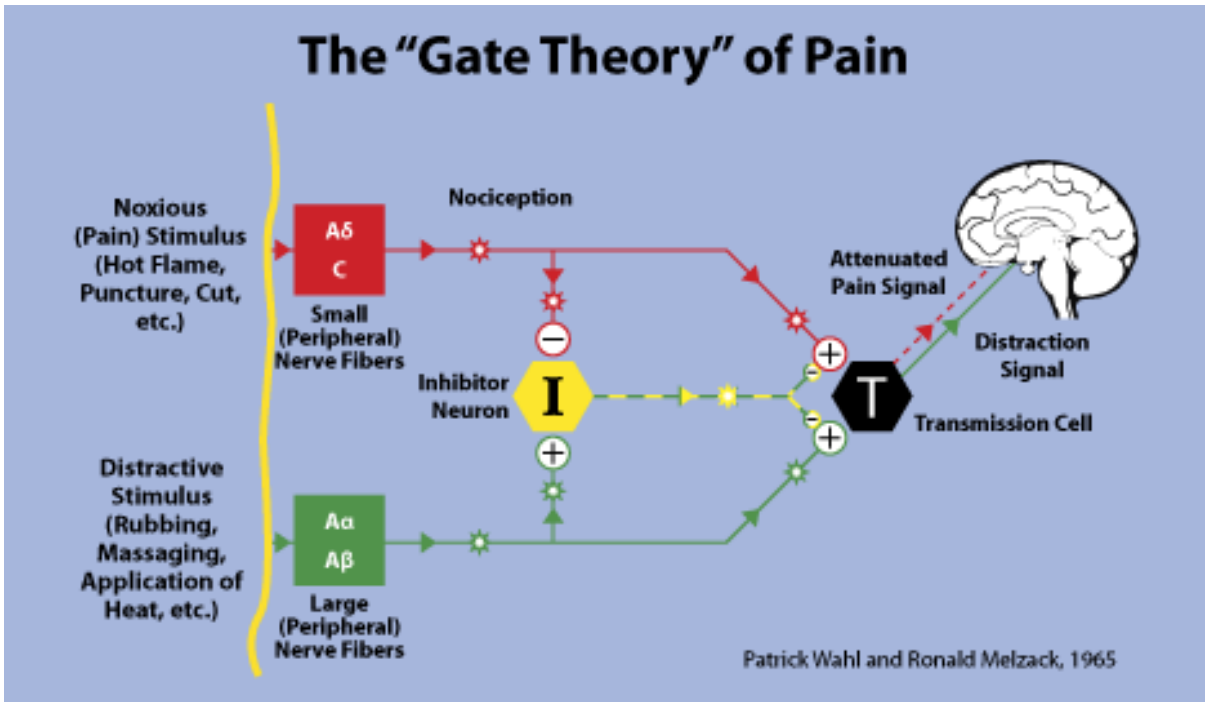
This is the most acceptable and debated theory of pain.It was proposed in 1965 by Melzack and Wall and is explained as follows; small myelinated sensory neurons carry afferent input to the dorsal horn of the spinal cord.Here substantia gelatinosa layer contains interneurons, which function as a gate to modulate sensory input to higher centres.

The opening and closing of this hypothetical gate is influenced by the following factors;

1.A stronger noxious input increases the amount of activity in pain fibres and opens the gate.

2.When noxious stimulus exists , any activity in large diameter fibres called Aδ fibres tends to close the gate.

3.The efferent descending pathways can either open or close the gate depending on the brain processes.To elaborate further, people who are distracted by competing environmental stimuli, may not notice the pain of an injury.



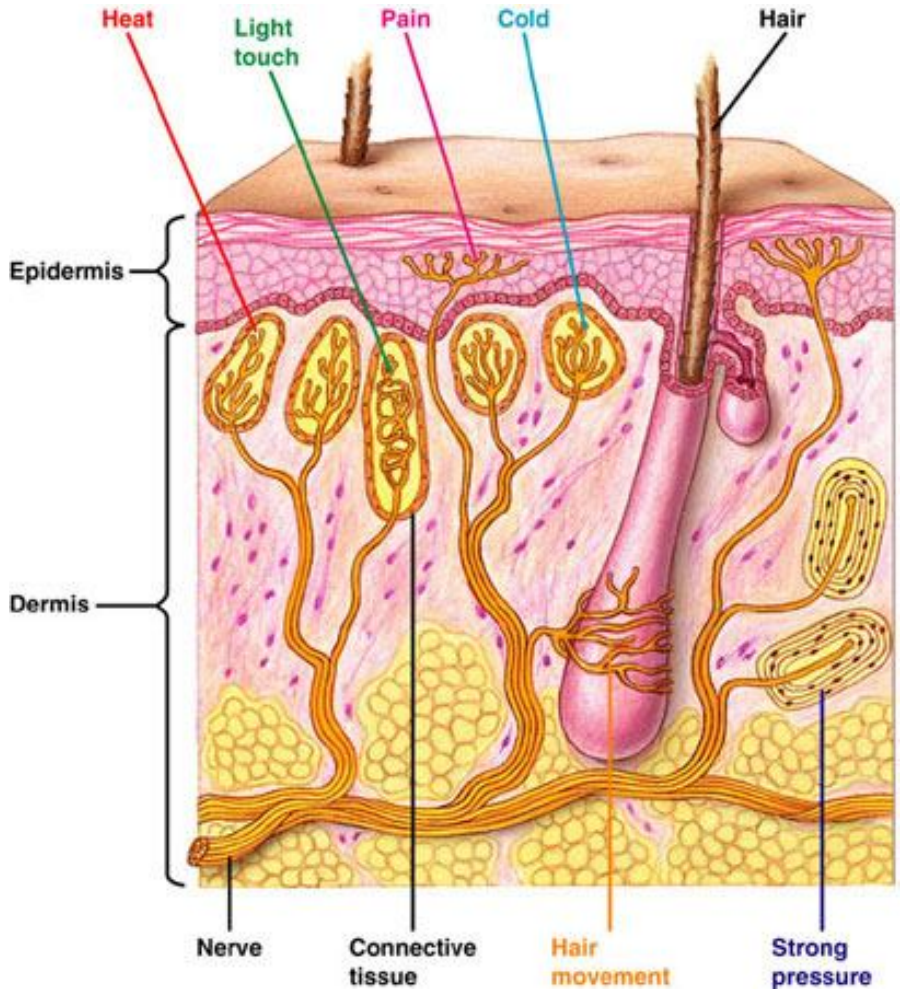
Fig(2); Gate control theory of pain

F. Epidemiology of pain(16):

The prevalence of under treated pain is found to be very significant worldover. In a survey in the United States, 1 out of 6 patients sought a physician with complain of pain.About 1/3 rd of patients develop chronic pain annually. Acute pain also accounts for more than 2/3rd visits to the Emergency Department.Management of pain , whether acute or chronic is given a low priority, especially in developing countries.There is an acute shortage of health resources and health professionals.In a publication by the International Narcotics Control Board (INCB), the global opioid consumption in the developed world is 87%,whereas in the developing countries it is only 13%.It is, in the developing part of the world that 4/5th of the world's population resides.

G. Receptors of pain(17)

Nociceptors are free nerve endings present in the skin, muscle, joints, bone and viscera.These contain transient receptor potential channels (TRP), similar to voltage-gated potassium channels or nucleotide-gated channels.They have 6 transmembrane domains, with a pore between 5 and 6.There is transduction of noxious stimuli into receptor potentials, which initiate action potentials in nerve fibres.This constitutes the afferent input towards higher centres.There are no nociceptors inside the central nervous system.



Fig(3); somatosensory receptors(18)

Types of nociceptors;

A) Skin nociceptors

Functionally divided into four categories

1.High threshold mechanoreceptors or specific nociceptors – They respond to intense mechanical stimulation.

2.Thermal nociceptors – They respond to intense mechanical stimuli and thermal stimuli.

3.Chemical nociceptors – These respond to chemical stimuli only.

4.Polymodal nociceptors – They respond to mechanical, thermal, and chemical stimuli.

B) Joint nociceptors

High threshold mechanoreceptors, polymodal nociceptors, and silent nociceptors are present in the joint capsule and ligaments.The innervating fibres contain substance P and CGRP (calcitonin gene-related peptide), which are the inflammatory mediators.

C) Visceral nociceptors

Organs contain mechanical, thermal, chemical, and silent nociceptors (mostly).They are scattered within variable distances of each other.

D) Silent nociceptors

Located in the skin and deeper tissues, these receptors become responsive upon injury or inflammation, apparently by reducing their threshold.They induce hyperalgesia, central sensitization and allodynia.

Nocineurons

Nociceptive neurons in the spinal cord.

1. High-threshold mechanoreceptors; activated by noxious cutaneous and visceral stimuli.The afferent fibres release glutamate and other neuropeptides, which sensitize dorsal horn neurons.
2. Chemical nociceptors; activated by chemical of thermal stimuli.
3. Thermal nociceptors; activated by chemical of thermal stimuli.
4. Polymodal nociceptors (WDR: wide dynamic range neurons)
   These respond to both noxious and non-noxious stimuli.

Rexed lamina I – This layer has nociceptive specific/ mechanoreceptors.Their function is to alerts for noxious stimuli.

Rexed lamina II – This layer is specific for wide dynamic range/ polymodal neurons.It analyses the parameters of noxious stimuli.

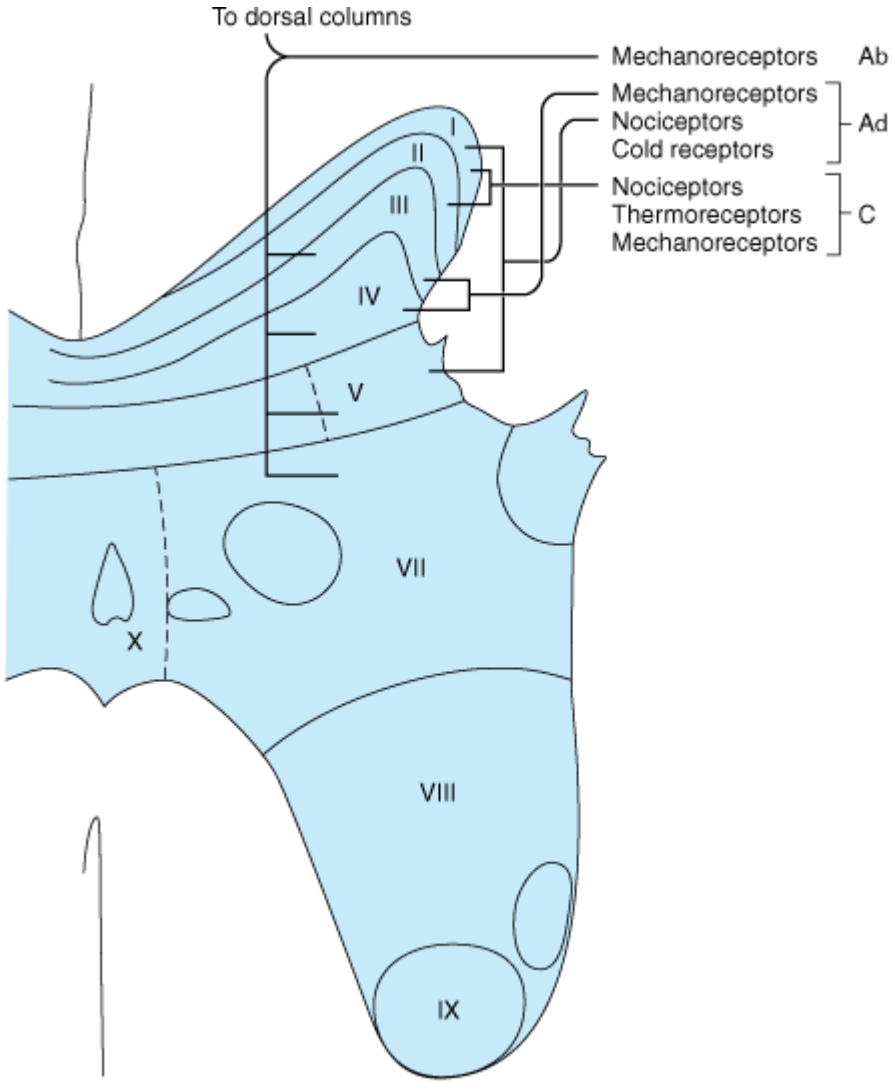
The C fibres are activated by substance P.

The Aδ fibres are sensitized by glutamate.

Table(4);Spinal Cord Lamina(10)

Lamina	Predominant Function	Input	Name
I	Somatic nociception thermoreception	Aδ, C	Marginal layer
II	Somatic nociception thermoreception	C, Aδ	Substantia gelatinosa
III	Somatic mechanoreception	Aβ, Aδ	Nucleus proprius
IV	Mechanoreception	Aβ, Aδ	Nucleus proprius
V	Visceral and somatic nociception and mechanoreception	Aβ, Aδ, (C)	Nucleus proprius; WDR neurons[1]
VI	Mechanoreception	Aβ	Nucleus proprius
VII	Sympathetic		Intermediolateral column
VIII		Aβ	Motor horn
IX	Motor	Aβ	Motor horn
X		Aβ	Central canal

[1]WDR, wide dynamic range



Fig(4); Rexed's spinal cord laminae.(10)

Factors activating nociceptors:

1.Globulin and protein kinases

2.Arachidonic acid – metabolized to prostaglandins, act via G protein, protein kinase. A cascade which blocks potassium efflux; thus making nociceptors more sensitive.

3.Histamine- released from mast cells .

4.Nerve growth factor (NGF)- this binds to TrkA receptors, activating them.

5.Substance P andd calcitonin gene-related peptide – Produce vasodilatation and edema.

6.Potassium- post injury there is evidence of elevated local extracellular potassium concentration.

7.Serotonin (5-HT), Acetylcholine (Ach), low pH (acidic) solutin and ATP

8.Muscle spasm and lactic acid

The release of all these substances sensitizes C fibres, reducing their threshold, which is referred to as peripheral sensitization.

Table(5); Major Neurotransmitters Mediating or Modulating Pain.(10)

Neurotransmitter	Receptor[1]	Effect on Nociception
Substance P	NK–1	Excitatory
Calcitonin gene-related peptide		Excitatory
Glutamate	NMDA, AMPA, kainite, quisqualate	Excitatory
Aspartate	NMDA, AMPA, kainite, quisqualate	Excitatory
Adenosine triphosphate (ATP)	P_1, P_2	Excitatory
Somatostatin		Inhibitory
Acetylcholine	Muscarinic	Inhibitory
Enkephalins	μ, δ, κ	Inhibitory
β-Endorphin	μ, δ, κ	Inhibitory
Norepinephrine	α_2	Inhibitory
Adenosine	A_1	Inhibitory
Serotonin	5-HT_1 (5-HT_3)	Inhibitory
γ-Aminobutyric acid (GABA)	A, B	Inhibitory
Glycine		Inhibitory

[1]NMDA, *N*-methyl-D-aspartate; AMPA, 2-(aminomethyl)phenylacetic acid; 5-HT, 5-hydroxytryptamine.

H. Modulation of nociception(10)(19)(20)

Peripheral modulation;

This type of modulation involves two basic mechanisms.

1. Primary hyperalgesia – This is the sensitization of nociceptors following release of allogens surrounding any tissue injury or inflammation.

   Examples of inhibitors of primary hyperalgesia are;

   Prostaglandin inhibitors = Aspirin, Non-steroidal anti inflammatory drugs(NSAIDs), COX inhibitors9COXIBs).

   Phospholipase A2 inhibition = Corticosteroids

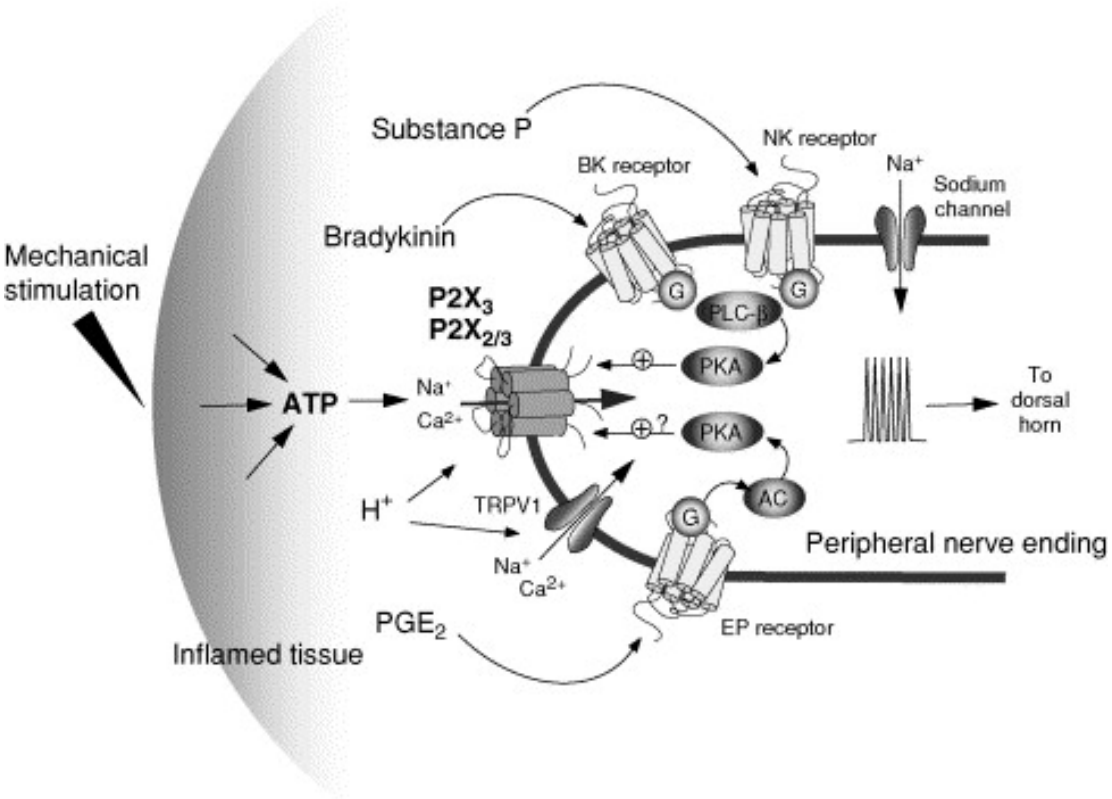
2. Secondary hyperalgesia – The triple response of neurogenic inflammation, which includes flare or red flush, local tissue edema and sensitization, primarily due to antidromic release of substance P and CGRP, leads to secondary hyperalgesia.

   Examples OF inhibitors of secondary hyperalgesia are;

   Topical application of capsaicin, degranulates and depletes substance P.

3. Miscellaneous peripheral modulators of pain-

   - Nociceptive sensory neurons have a calcium channel receptor known as Vanilloid or TRPV-1 receptor.
   - Tetrodotoxin-insensitive sodium channels NAv 1.8 and NAv1.9.



Fig(5); peripheral pain modulation

Central modulation of pain:

Facilitation mechanism;

This modulation works around three mechanisms:

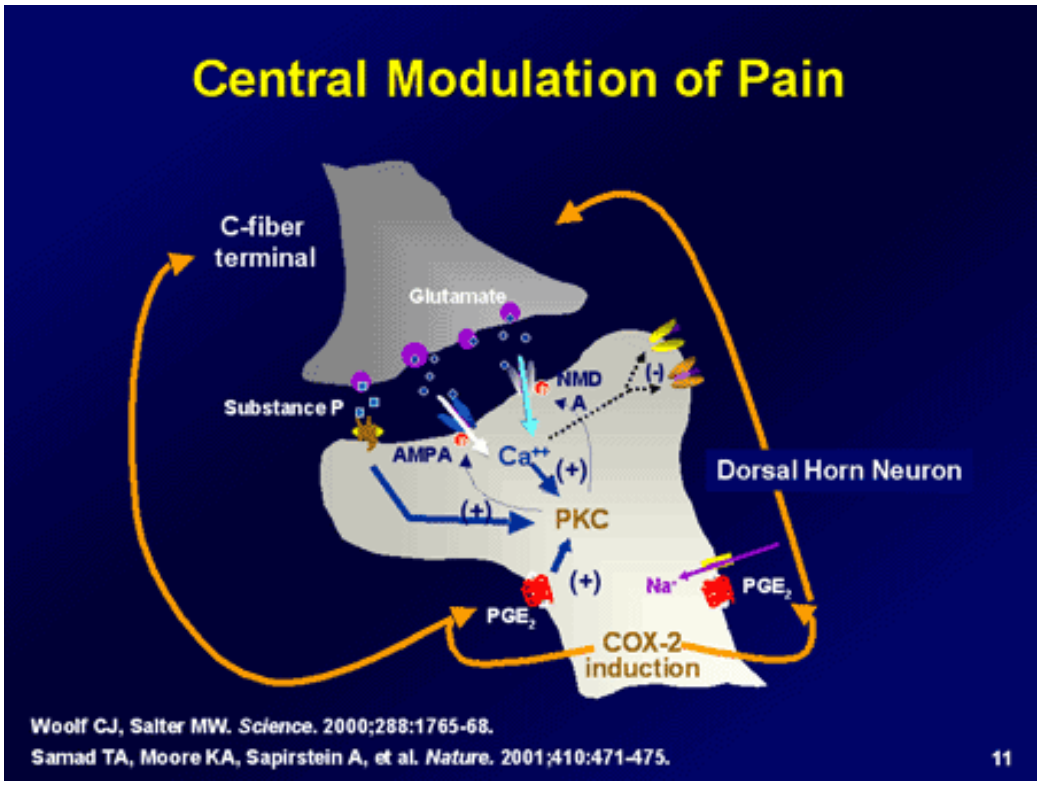
1.A prolonged repetitive stimulus increases the discharge frequency of Wide Dynamic range, second-order neurons.This activation continues even after cessation of the inciting C fiber input.

2.There is expansion of the sensitive area around dorsal horn neurons, such that adjacent unresponsive neurons also get sensitized.These, now become capable of responding to noxious and non-noxious inputs.

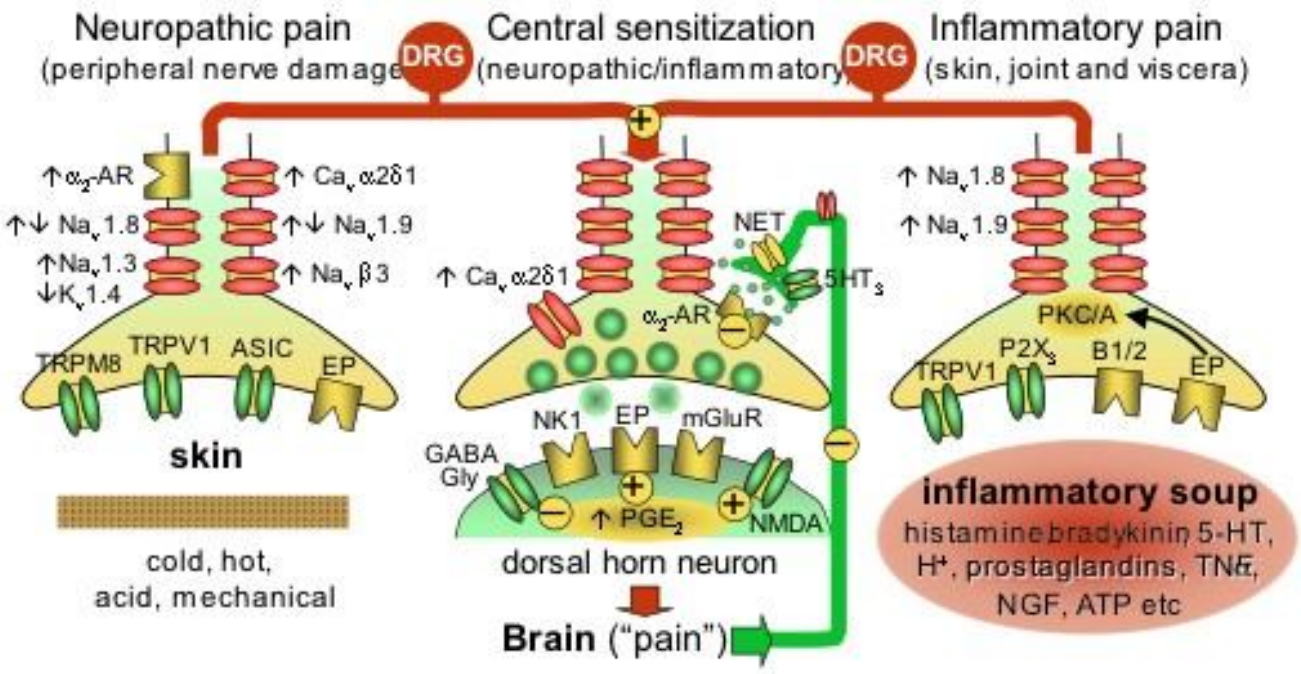
3.There is bilateral exaggeration of flexion reflexes.

Neurochemical mediators include; Substance P, Calcitonin gene-related peptide(CGRP), Vasoactive intestinal peptide(VIP), Cholecystokinin, Angiotensin, Galanin, L-glutamate,and L-aspartate.

Common pathway is interaction with Gprotein-coupled receptors.



Fig(6); Central pain modulation(21)



Fig(7); Mechanism of central sensitization

Inhibition mechanism;

Segmental inhibition;

Glycine and GABA are inhibitory neurotransmitters that regulate this mechanism.

GABA-A – This creates inhibition by increasing ,Cl^- channel conductance.Example of agonist is muscimol.Glycine shares the same mechanism.

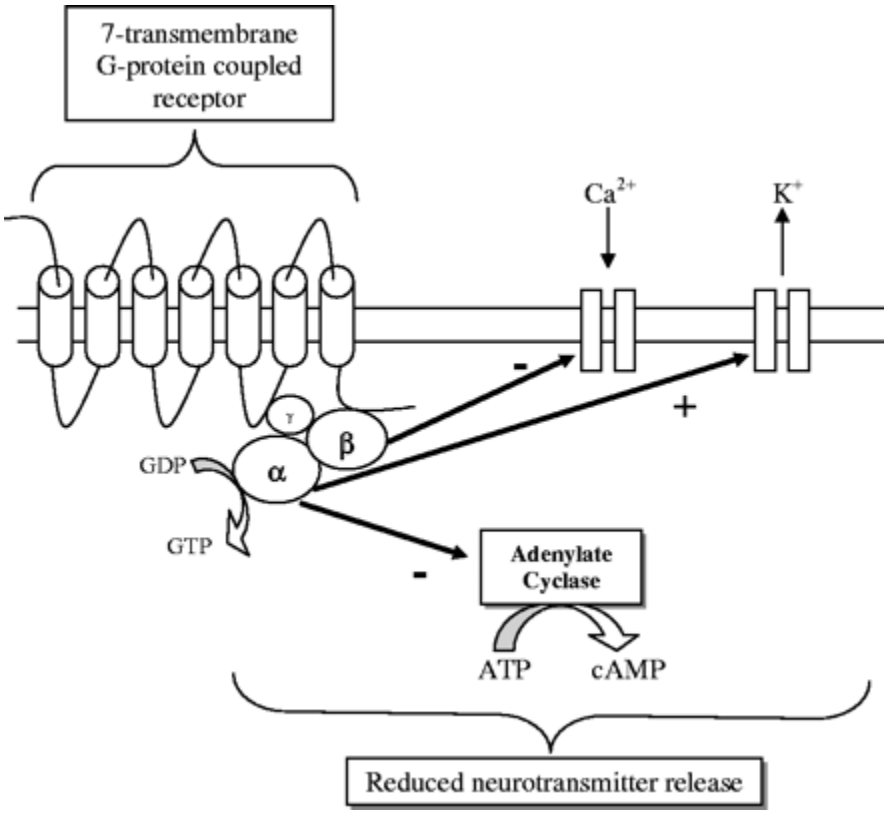
GABA-B – This increases K+ conductance,causing segmental inhibition.The agonist is baclofen.

Glycine – It is excitatory on NMDA receptors.The antagonists are strychnine and tetanus toxoid.

Adenosine – A1 receptor– inhibits adenylcyclase causing antinociceptive.

Its antagonists are phosphodiesterase inhibitors.

A2 receptor – stimulates adenylcyclase.



Fig(8);(22) G-protein coupled receptor

It is a seven transmembrane protein receptor, which upon activation transduces a sequence of intracellular changes like potassium efflux, inhibition of adenylylcyclase enzyme.There are three subunits α, β, γ, and the α-subunit binds to adenylate cyclase and potassium-calcium channel.

I. <u>Endogenous opiate system</u>(10)

This system involves the nucleus raphe magnus and reticular formation.

These endogenous opioids are:

a.Methinine enkephalin

b.Leucine enkephalin

c.βeta-endorphin

Antagonist is naloxone.

They cause pre-synaptic and post-synaptic inhibition, by inducing hyperpolarization.

(NOTE:Exogenous opioids act only post-synaptically in Substantia gelatinosa)

J. <u>Pain pathways</u>(23)

There are three major ascending pathways , which carry afferent input of pain to higher centres.

<u>Neospinothalamic tract</u>

This constitutes the classic lateral spinothalamic tract.

First order neurons

➢

Dorsal root ganglion

➢

Synapses in rexed layer I / marginal zone

➢

Decussate in anterior white commissure/ same level

➢

Ascend in anterolateral column

➢

Ventroposterolateral and ventoposteroinferior nucleus thalamus/ relay station

➢

Primary somatosensory cortex

Fibres below neck travel to

➢

VPL AND VPI nuclei

➢

Fibres from head and neck

➢

Trigeminothalamic tract

➢

Ventroposteromedial – Somatosensory cortex I / Brodman area 1/ Aδ fibres

&

Intralaminar nuclei – Somatosensory cortex II / Brodman area 2/ C fibres

Paleospinothalamic tract

(Phylogenetically old)

Nociceptive neurons/ wide dynamic range (WDR)

➢

Dorsal root ganglion

➢

Synapses in rexed layer II (Substantia gelatinosa), IV-VII & X

➢

Crossed and uncrossed fibres bilaterally

➢

Mesencephalic reticular formation(MRF) & periaqueductal gray(PAG)

➢

Spinoreticular tract

➢

Tectum

➢

Spinotectal & Spinomedullary tract

➢

PF-CM (IL) complex/ parafasiculus-centromedian thalamus

➢

Anterior Spinothalamic tract

➢

Somatosensory cortex II – Brodman area 3

Paleospinothalamic tract also activates brainstem nuclei for the descending pain suppression pathway.

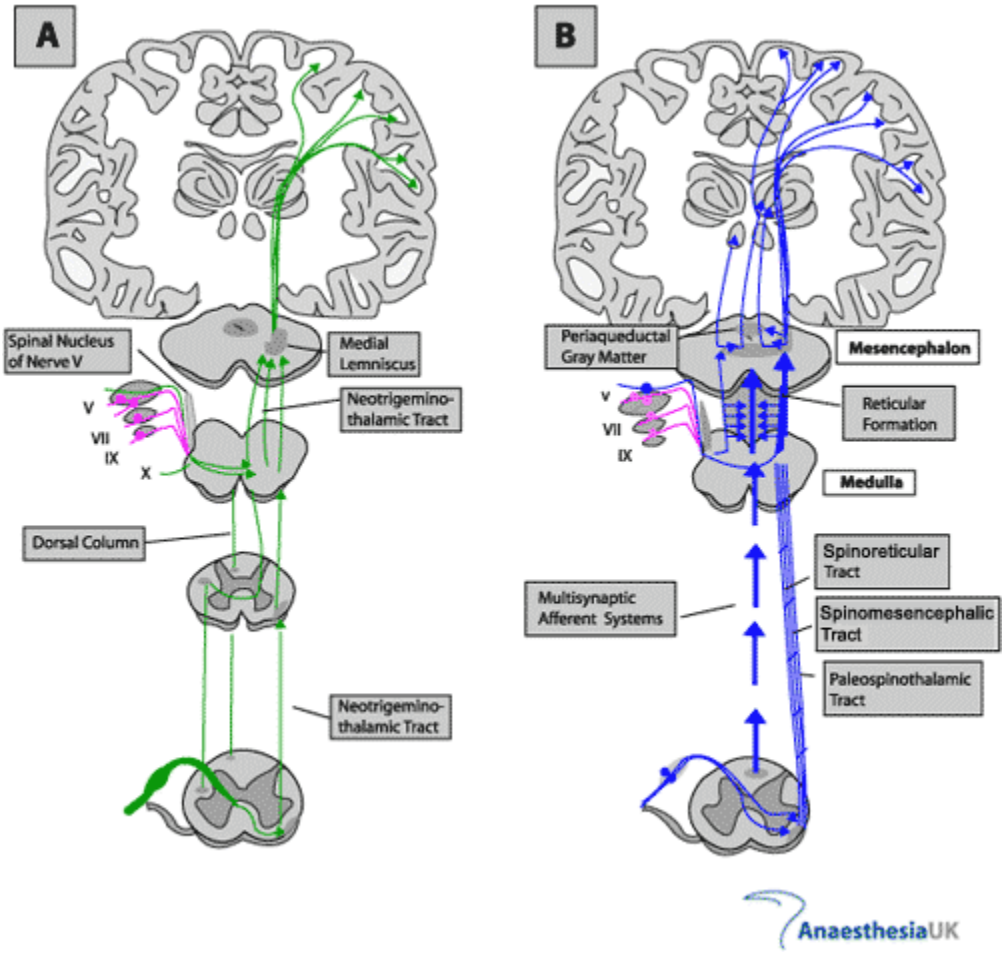
The intralaminar nuclei and limbic system, which processes the emotional component of pain, are extensively well connected.

Archispinothalamic tract

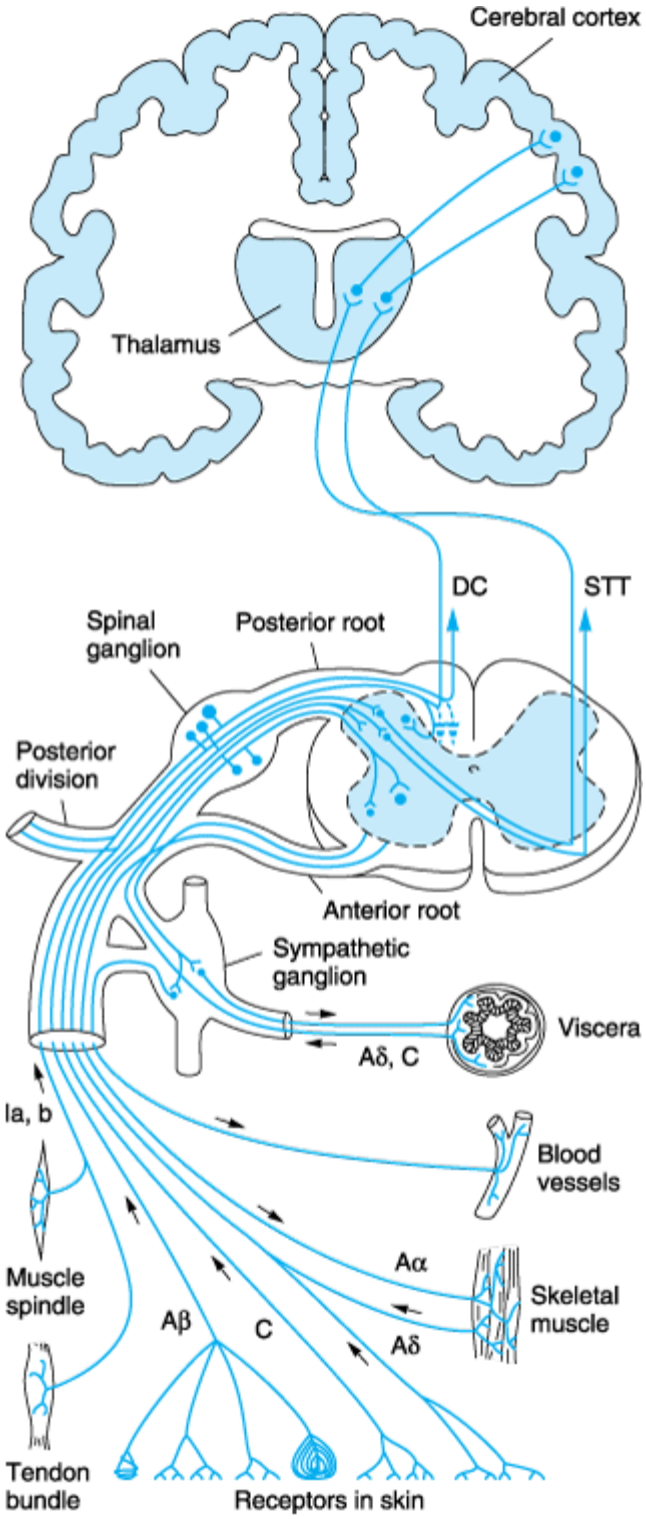
(Phylogenetically oldest tract)

Nociceptors in Dorsal root ganglion
➢
Rexed layers II, IV-VII
➢
Multisynaptic propriospinal diffuse pathway/ bilaterally
➢
MRF & PAG area
➢
PF-CM complex
➢
Hypothalamus and limbic system

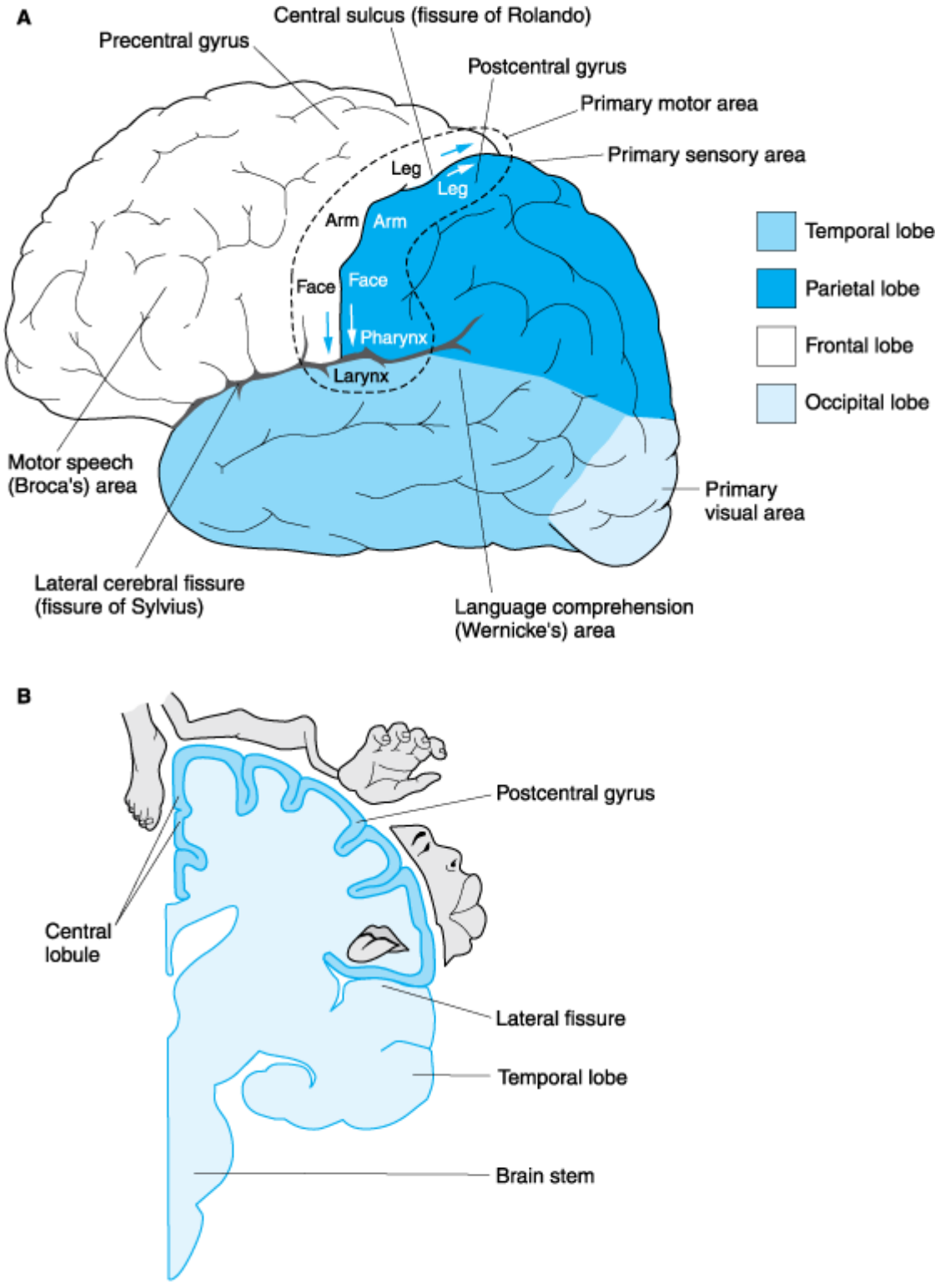
This tract is responsible for visceral, emotional and autonomic components of pain.



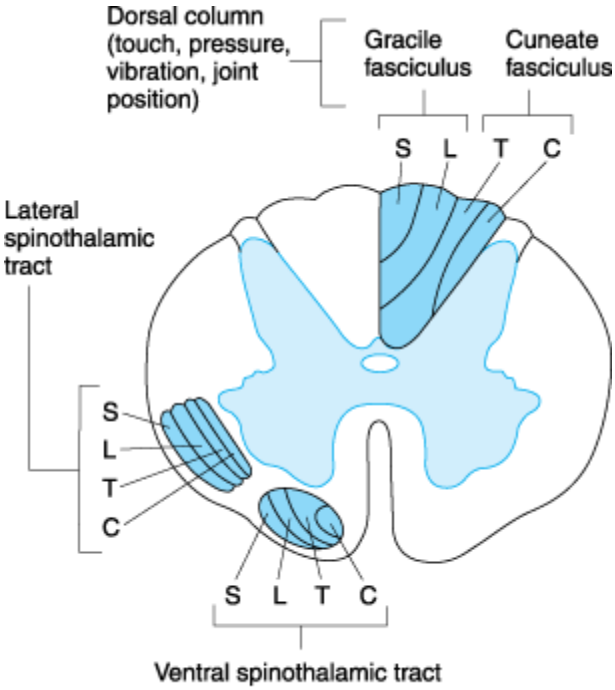
Fig(9); Pain pathways



Fig(10); Pain pathway II



Fig(11); Primary sensory cortex & homunculus



Fig(12); spinal cord cross-section depicting spinothalamic and other ascending pathways, with spatial distribution of fibres from different spinal levels.

K. <u>Endogenous pain suppression pathway</u>:(24)

The studies of Magoun and colleagues, provided evidence that the brainstem exerts an inhibitory control over spinal cord input.

This concept was further supported by the animal experiments of Reynolds in 1969.

There are three components, that constitute this pathway.

1) Midbrain periaqueductal grey (PAG)

This area has high density of opiate receptors and connections with spinal cord and nucleus raphe magnus.

Triggers like direct electrical stimulation, opiates and acupuncture activate a descending inhibitory pathway via raphe magnus and locus coeruleus, that inhibits pain pathways.

2) Nucleus raphe magnus

Situated in rostral medulla, it is rich in serotonin and projects axons onto marginal nucleus for generating synapses, that inhibit pain signals.

3) Nucleus locus coeruleus

Located in the floor of fourth ventricle,has high levels of norepinephrine, follows the same route as axons from nucleus raphe magnus.

L. <u>Physiological sequelae of pain</u>:

Any acute injury in the form of surgical procedure or otherwise, puts all our organ systems under undue stress.The catabolic processes, which get activated prove deterent in recovery.These changes are especially harmful for patients with pre-existing co-morbidities.The combination of both factors, considerably increase their postoperative morbidity.The state of nutrition plays a major role in convalescence.

The effects on each system are as follows:

1.Respiratory system

The effect depends upon the site of surgery.Those involving the abdomen lead to dysfunction of the diaphragm, decreased Functional residual capacity and paradoxical respiration.There is a decrease in the lung compliance and increase in the work of breathing.The patient becomes tachypneic, hypoxic, hypoxemic, hypercapnic,with a ventilation perfusion mismatch and atelectasis.There is increased predisposition to develop pneumonia.

2.Cardiovascular system

The sympathetic stimulation leads to release of many mediators of stress like catecholamines, activation of rennin-angiotensin system leading to release of Angiotensin and aldosterone.All these increase the workload on the heart, disrupts the myocardial demand-supply balance.Patient can develop dysrhythmias, angina, congestive cardiac failure and myocardial infarction.

3.Endocrine system

There is an increase in the catabolic hormones and a reduction of anabolic ones.The increase in adrenocorticotropic hormone, cortisol, epinephrine and glucagon lead to protein breakdown, lipolysis and hyperglycemia.The increased antidiuretic hormone and aldosterone lead to salt and water retention.Furthermore;the increased levels of cortisol, catecholamines and angiotensin-II can lead to congestive heart failure.

4.Stress following surgery depresses the immune system and predisposes the patient to infections.There is decreased activity of the reticuloendothelial system with decreased killer T-cells.

5.Effects on coagulation

There is activation of the coagulation cascade and decrease fibrinolysis.

6.Gastrointestinal system

The sphincter tone increases and there is gastroparesis.Postsurgical stress increases the incidence of PONV.

7.There is retention of urine.

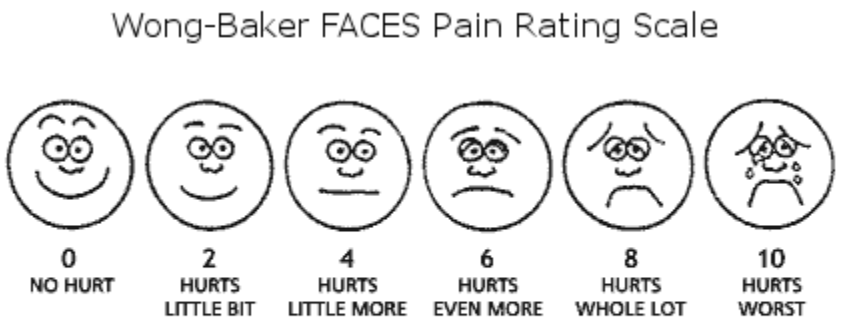
M. Pain Assessment Scales:(25)

The National Initiative on Pain Control (NIPC) has provided us various pain assessment tools.A brief description follows:

Wong-Baker FACES pain rating scale

This is recommended for patients older than 3 years.

Instructions- Ask the patient to choose the face that best describes his/her pain.



From Wong D.L., Hockenberry-Eaton M., Wilson D., Winkelstein M.L., Schwartz P.: Wong's Essentials of Pediatric Nursing, ed. 6, St. Louis, 2001, p. 1301. Copyrighted by Mosby, Inc. Reprinted by permission.

Fig(13); Wong-Baker FACES pain scale

0-10 NUMERIC PAIN RATING SCALE

To assess subjective intensity of pain.

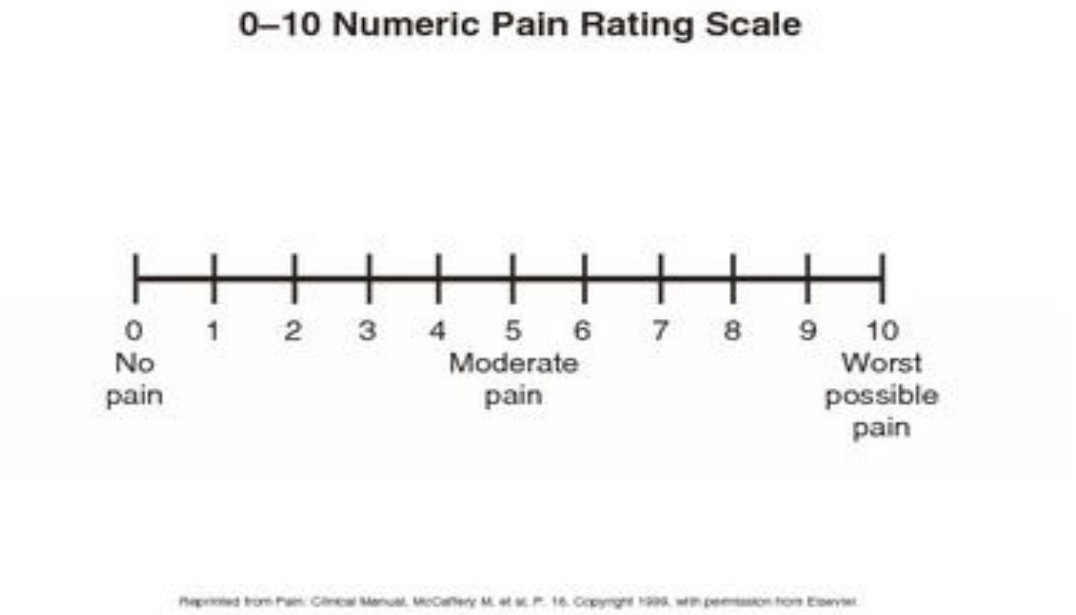
To be used in ages 18 and above.

The numbers correspond to pain level as follows:

1-3 = Mild pain

4-6 = Moderate pain

7-10 = Severe pain



Fig(14); Numeric pain scale

<u>McGill Pain Questionnaire</u>

This is also called as McGill pain index, and was developed at McGill University by Melzack and Torgerson in 1971.

It has been used in children as young as five years of age.

Instructions:

Circle the words that describe your pain only one word in a group.After this circle the three words in groups 1-10, relating your pain.pick two words in 11-15,one word in 16, and one in 17-20.Finally you should have seven words in total, describing your pain intensity and quality.

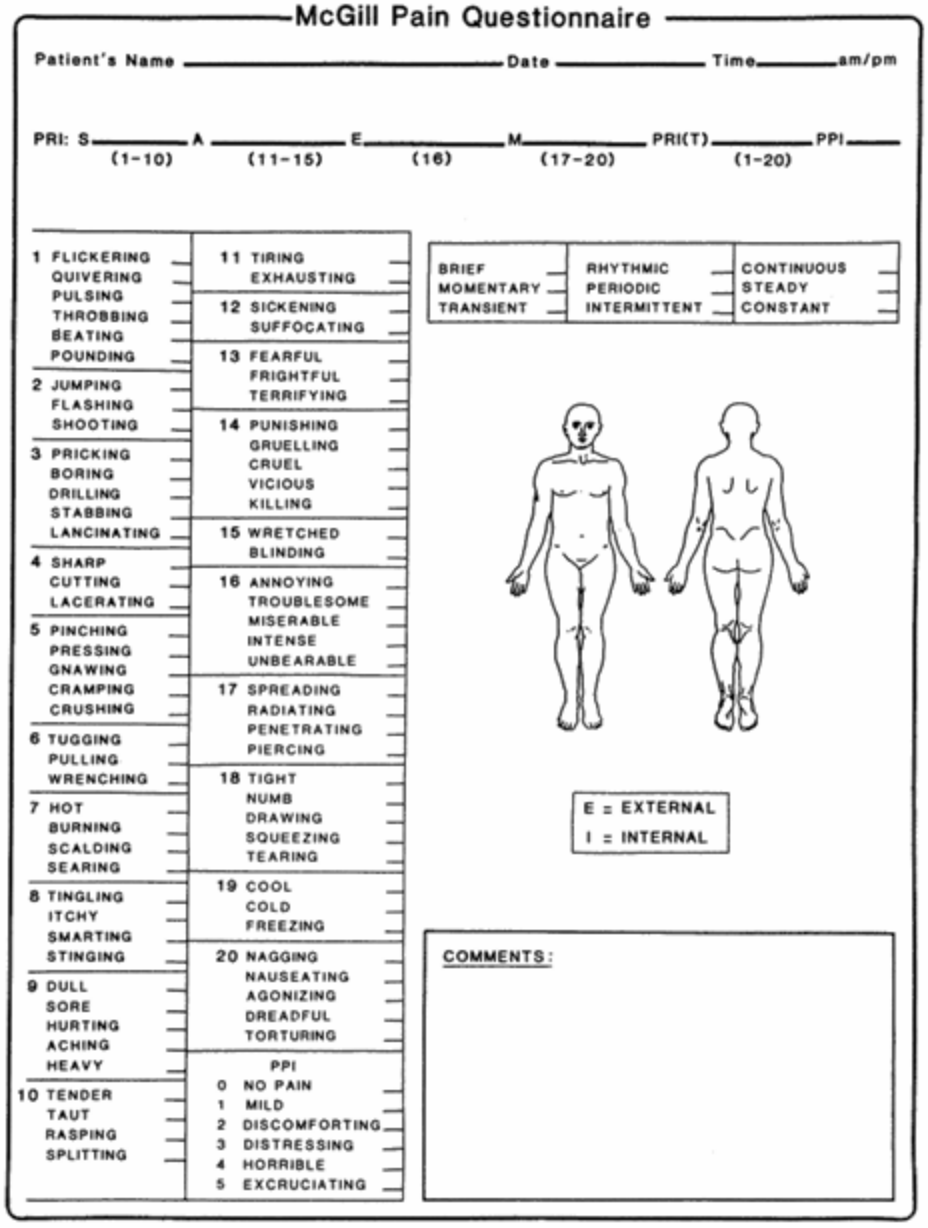


FIG. 2. McGill Pain Questionnaire. The descriptors fall into four major groups: sensory, 1 to 10; affective, 11 to 15; evaluative, 16; and miscellaneous, 17 to 20. The rank value for each descriptor is based on its position in the word set. The sum of the rank values is the pain rating index (PRI). The present pain intensity (PPI) is based on a scale of 0 to 5. Copyright 1970 Ronald Melzack.

Fig(15); McGill Pain Questionnaire

Behavioural Rating Scale

- Use with non-verbal patients
- Add scores together
- Document total pain score out of 10

For patients unable to provide a self-report of pain: scored 0–10 clinical observation

Face	0 Face muscles relaxed	1 Facial muscle tension, frown, grimace	2 Frequent to constant frown, clenched jaw	Face score:
Restlessness	0 Quiet, relaxed appearance, normal movement	1 Occasional restless movement, shifting position	2 Frequent restless movement may include extremities or head	Restlessness score:
Muscle tone*	0 Normal muscle tone	1 Increased tone, flexion of fingers and toes	2 Rigid tone	Muscle tone score:
Vocalisation**	0 No abnormal sounds	1 Occasional moans, cries, whimpers and grunts	2 Frequent or continuous moans, cries, whimpers or grunts	Vocalisation score:
Consolability	0 Content, relaxed	1 Reassured by touch, distractible	2 Difficult to comfort by touch or talk	Consolability score:
Behavioural pain assessment scale total (0–10)				/10

Functional activity score#
(Cough/movement)
A – No limitation
B – Mild limitation
C – Severe limitation
#Relative to baseline

* Assess muscle tone in patients with spinal cord lesion or injury at a level above the lesion injury. Assess patients with hemiplegia on the unaffected side.
** This item cannot be measured in patients with artificial airways.
Table(6); Behavorial Rating Scale

Functional Activity Score

This is an activity related score;

A – No limitation meaning the patient's activity is unrestricted by pain

B – Mild limitation means the patient's activity is mild to moderately restricted by pain

C - Severe limitation means the patient ability to perform the activity is severely limited by pain

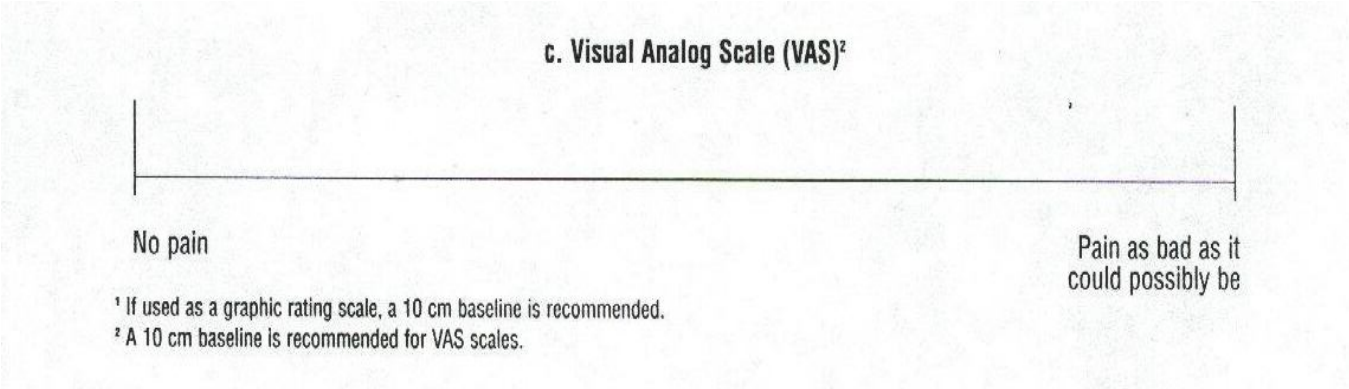
*Relative to baseline, refers to any restriction above pre–existing condition the patient may already have.

Visual Analog Scale

This scale is a 10cm line, on which patient is asked to rate their current level of pain.

It is applicable from five years of age.

The initial mark is used as a baseline for subsequent comparisons, for an individual.



Fig(16); VAS Pain Scoring System

Universal Pain Assessment Tool

This tool is intended to assist health care providers in assessing pain according to individual patient needs.

The 0-10 scale is used for patient self-assessment.likewise the faces and behavorial scales are for those, who cannot express their pain intensity.

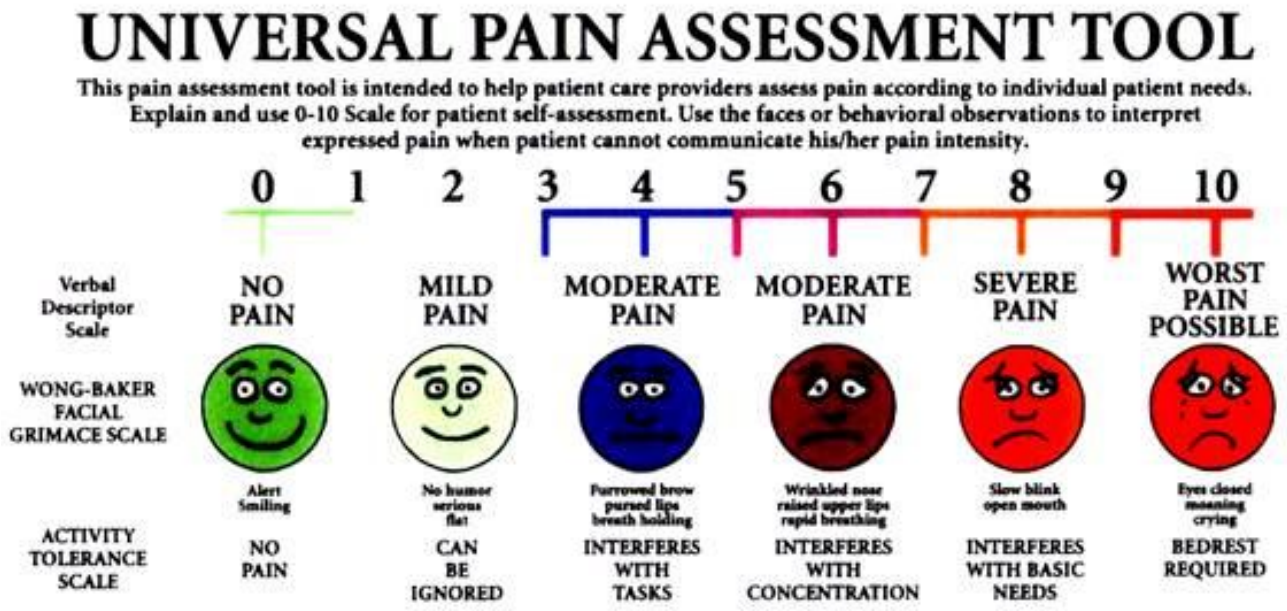


Figure (17). Universal Pain Assessment Tool, incorporating 0 to 10 Scale, Verbal Descriptor Scale, Wong-Baker Facial Grimace Scale, and Activity Tolerance Scale.

N. <u>Preemptive Analgesia</u> (26)(27)(28)

Preemptive means ‘Preventive and not ‘before the incision.

The nociceptive input undergoes central and peripheral modulation .This processing of afferent impulses amplifies postoperative pain.Preemptive analgesia is a modality of antinociceptive treatment , which is thought to modify this mechanism.

This concept was first introduced by Crile in the 19th century, and further developed by the animal experiments of Woolf.

Crile used regional blocks with general anaesthesia to inhibit the initiation of intraoperative nociception and thereby prevent the formation of painful postoperative scars.These scars are induced by the alteration in central nervous system plasticity.

Central sensitization-Is defined as, the hypersensitivity to pain due to persistent post injury changes in the central nervous system plasticity.

Central hyperexcitability-When a normal afferent input ellicits an exaggerated and prolonged response from the neurons, following tissue damage, it is referred to as central hyperexcitability.

Preemptive analgesia can be broadly explained as, that antinociceptive treatment that prevents, central sensitization from incisional and inflammatory injuries.It starts from before the incision and continues throughout the duration of surgery ,into the initial postoperative period.In all this the inflammatory component can be a very dominating factor.

Preemptive analgesia reduces pathological pain.

Central sensitization to pain follows three components in series:

1.Preoperative pain and other noxious inputs.

2.Noxious intraoperative stimuli

3.Postoperative inflammation and neural activity.

Wall coined the term ‘pre-emptive preoperative analgesia’

O. Effects of anaesthesia on surgical stress(20)

General anaesthesia

This does not attenuate the neuroendocrine stress response. An exception to this, are very high-dose opioids, which can inhibit stress response to some extent.

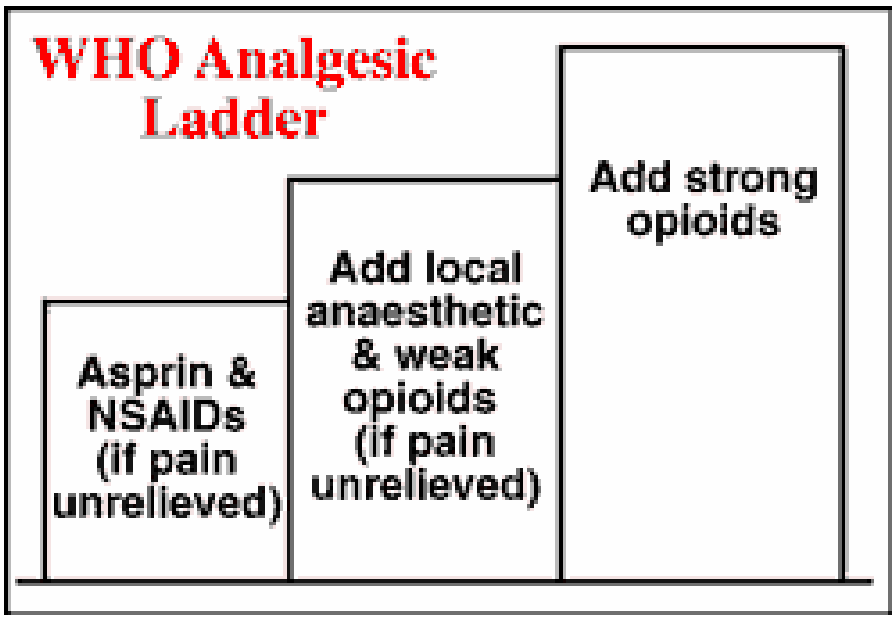
Inhalational anaesthetics with MAC value > 1.5 MAC, suppresses only intraoperative catecholamine release.

Regional Anaesthesia

These techniques can ablate stress response, but the exact respose is influenced by various factors;

- Multimodal techniques appear more efficacious.
- Effective level of antinociception before surgery – All the afferents to the operative site need to be blocked.A block below L1, is proven to be ineffective in attenuating the cortisol response.
- Continuation of antinociceptive modality, well into the postoperative period
- Timing of analgesia – Preferably before the inciting stimulus.
- Individualization of therapy, tailored to patients body habitus and co-morbidities.

P. <u>WHO Analgesic Ladder</u>:(29)



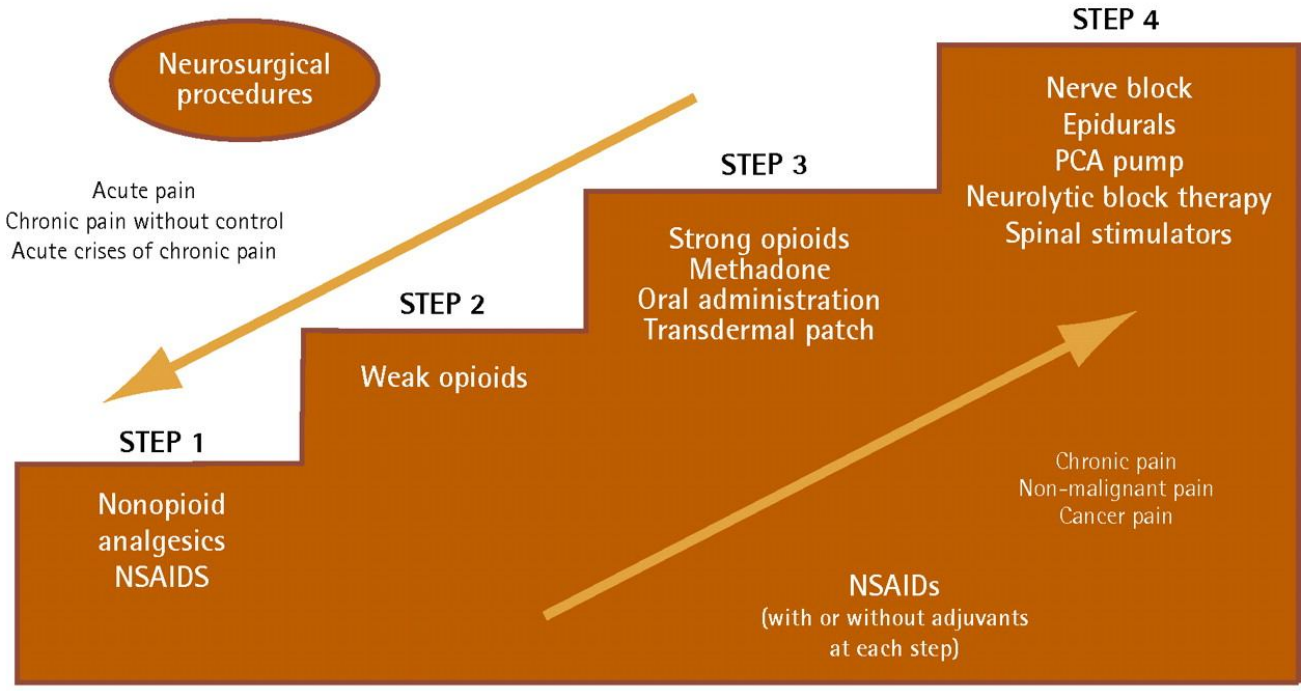
Fig(18); The World Health Organisation Analgesic Ladder introduced for improving pain control in cancer patients. Originally described, the ladder has three rungs.

This is a step-wise approach, to increase Analgesia in the face of unrelieved pain.It was initially devised for cancer pain management, but its application to acute pain was well founded.It is a tool to guide healthcare providers, by providing rough protocol of multimodal analgesia.Step I is for treatment of mild pain with non-opioid analgesics.Step II deals with moderate pain with weak opioids, with or without the addition of non-opioids.In Step III, severe pain is handled with strong opioids with or without non-opioids.There is provision to add adjuvants at each step.

This pain ladder does not have any specifications for the name of drug to be used, in order to maintain a level of flexibility according to the protocols and availability in the area.The limitation of this ladder is that its applicability seems more for slowly progressing pain and not initially severe pain.Severe pain would need strond opioids from the very beginning.Another problem faced was with Step II, that was not found to be effective.

<u>Modified WHO Analgesic Ladder</u>: (30)

Figure 2. New adaptation of the analgesic ladder



NSAID—nonsteroidal anti-inflammatory drug, PCA—patient-controlled analgesia.

Fig(19); New adaptation of analgesic ladder

This is a modification from the original ladder, in an effort to overcome the shortcomings. It is also based on the concept of multimodal analgesia.

It depends on the availability of strong opioids in the area and trained physicians to administer them.

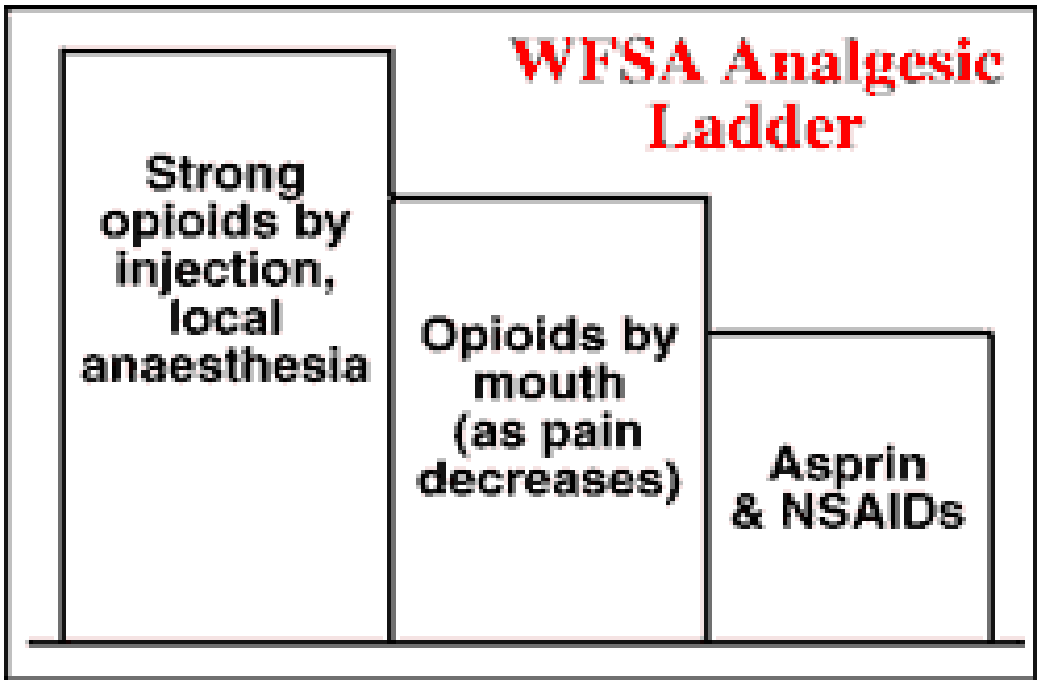
The same three step approach has been maintained..

In Step I non-opioid is started for mild pain, if pain persists then a titrated low doe of strong opioid is added to the regimen.For moderate pain in Step II ,treatment begins with low dose strong opioids, with or without non-opioids.If the pain is severe, for Step III strong opioids is the norm; but this ladder creates a provision for nerve blocks and adjuvant therapy also.Such invasive procedures can be undertaken at any stage to treat moderate to severe pain.The use of weak opioids is being restricted, as not found to be efficacious.

There are recommendations to make the ladder more efficacious:

1) Whenever permissible,oral route for analgesics is preferred.
2) Analgesics be given at regular intervals.
3) Pain medication should be prescribed only after assessment of pain intensity with a standardized tool.
4) Dosing should be individualized.
5) Attention to detail is a must.

The World Federation of Societies of Anaesthesiologists (WFSA), has developed another analgesic ladder to manage acute pain.



Fig(20); WFSA Ladder for Acute Pain (29)

This is different from WHO Analgesic Ladder in that, it is a step-down approach to manage acute pain.This is apparently because the treatment of acute pain begins with more sturdy techniques, since afferent nociceptive input is stronger at the inception of the insult.As the wound heals,intensity of pain reduces so medications can be decreased. The route of administration is mostly parenteral on the first postoperative day.

On the second rung of the ladder, if oral intaken is allowed depending on the nature of the surgery, oral analgesics are added.The pain intensity also diminishes over time ,so strong opioids may not be needed by the patient.Susequently, peripherally acting non-opioid drugs might suffice as in the Step III.

Q. <u>Multimodal Analgesia</u> (31)(32)

It is an approach to manage postoperative pain, by combining multiple medications as well as procedures. The idea is to harness their analgesic synergism and decrease the individual dosages and hence their side-effects.

This therapy involves nociceptive stimulus and input inhibition at various levels.It can be initiated from the periphery through to the higher processing centres.

It should form an integral part of the pre-anaesthetic plan.

This method combines peripheral and central treatment of pain, along with preemptive analgesia.

Examples(33) of drugs acting at various concerned levels, which can be combined are as follows:

<u>Peripheral level</u>:

- **Local anaesthetics** – The use of Local anaesthetics in a peripheral way is mostly by wound infiltration, meant for minor to moderate procedures.The effect depends on the technique of infiltration as much on the type of drug used.Clinically it appears to have a short acting effect only, so is low on efficacy.The combining of this method with other analgesics seems very rational.

- **Non-steroidal inflammatory drugs**-The addition of these drugs have evidence to prove, the benefit in reducing opioid side-effects by reducing dosage.These can be used in a fixed dose combination with local anaesthetics, opioids also.There are a group of patients who need careful assessment before administereing NSAIDs.High-risk patients are those who are hypovolemic, in renal failure, active gastric ulcer, duodenal ulcer or any bleeding diathesis.
- **Opioids**-After any injury, the inflammation that sets in, causes expression of opioid receptors at the peripheral nerve endings.The application of morphine, for example exerts its analgesic effect via this mechanism.
- **Peripheral nerve blocks with local anaesthetics**- Local anaesthetics for nerve blocks are being combined with many adjuvants to increase their efficacy.Examples are like clonidine and ketamine.
- **Alpha-2 adrenergic agonists**- as mentioned above.

  Spinal cord level
- **Local anaesthetics**- The poststimulation discharge or wind-up of dorsal horn
- neurons is inhibited by **combination of local anaesthetics and opioids**.There are similar mechanisms being deduced for the action of clonidine, carbacol, and midazolam.
- **Opioids**
- **Alpha-2 agonists**

<u>Cortical level</u>

- **Opioids**

A Note(34) on **NMDA (N-methyl-D-aspartate antagonists)**

1.Ketamine- This well known general anaesthetic has been found to be anti-nociceptive in especially low doses.This effect is enhanced when used in combination with opioids, local anaesthetics, in a multimodal aspect.The psychomimetic side-effects are also negligible at this dose treatment.

2.Magnesium-This NMDA blocker has conflicting reports.High-doses seem to be opioid-sparing.

Gabapentin-type drugs

Pregabalin:This binds to voltage-gated calcium-channelin the central nervous system.They have a proven opioid-sparing effect, but they are associated with sedation.

Glucocorticoids

These have a definite role in reducing inflammation.

Aims

1) Decrease the side-effects of analgesics.

2) Prevent central sensitization, which can transform acute into chronic pain.

3) Early hospital discharge and rehabilitation.

4) To address pain as part of daily follow-up of patients.

Evidence-based combinations are as follows:

Intravenous opioids with NSAIDs, COXIBs, or acetaminophen.

Epidural or intrathecal opioids; with local anaesthetics,

- with clonidine
- with IV opioids
- with ketorolac
- with ketamine

R. APS (Acute Pain Services) (35)

The concept of acute pain services was first published by Brian Ready in 1988 in Seattle.In 1990 the Joint Colleges Report was published which recommended the initiation of Acute Pain Services worldwide.

These services form an integral part of Good Practice in any hospital, to provide safe and effective pain management.

'Pain Management Services: Good Practice', is a joint publication by the Royal College of Anaesthetists and the British Pain Society, May 2003.

The recommendations of this report form a sound basis for the working of an effective pain service.

The salient features are as follows;

1) All hospitals who deal with patients in acute pain, need a separate pain service.

2) Such services require multidisciplinary personnel like medical, nursing, pharmacy staff and physiotherapists.

3) The hospital should have its own pain protocols based on Evidence-based guidelines.

These Protocols should have provision for the following:

- Patient information (non-English speakers also)
- Pain management for neonates, children, elderly, mentally challenged,
- Communication difficulties, physical or cognitive impairment and drug abuse.
- Equality of services to all patients.

4) All healthcare professionals should undergo a graded, continous education and training programme in pain management.

5) These services need the support of the administration to build itself .It requires economic infrastructure, staffing, equipments, which need updating with newer developments.

6) Acute Pain Services need a responsible named consultant as the Director,with trained consultants working on various programmes.

7) This service should be available 24 hours in the hospaital.

8) A close liason should be established between these services and other specialities.

9) A regular service evaluation using tools like audits for efficacy, training, and complications should be performed.

{Adapted from The Royal College of Anaesthetists ■ Guidelines for the Provision of Anaesthetic Services}

S. PHARMACOLOGY OF ANALGESICS (Relevant to this study)

The word analgesic is a derived from greek word,meaning, an (“without”) and algos(“pain”).

Opioids

This class of drugs have a prime role in management of pain.They act on μ receptors, located centrally and peripherally.Their use is limited either by development of tolerance or associated side-effects.There is no ceiling effect, as far as analgesia is concerned.The common side-effects are:

- Pruritis
- sedation
- Respiratory depression
- Nausea
- Vomiting
- Constipation
- Urine retention

There are various routes of administration like; oral, intramuscular, intravenous, subcutaneous, transdermal patch, transmucosal, intrathecal, epidural space and topi0cal. The serum level can vary with the site, like wider variability with intramuscular route than intravenous.There is wide interindividual variability in the analgesic effect.For postoperative patients parenteral route is preferred because of the rapid onset of effect compared to other routes and also the nature of surgery precludes nil per oral state.The changeover from parenteral to oral route requires that an adequate level of analgesia be created with the parenteral route, which should be superimposed with oral analgesics.

The prescription of prn opioids breaks the analgesic cycle regularly, needing rescue medications.So the use of sustained release formulations is advocated.They maintain constant drug levels in the bloodstream.

Transdermal patch acts as an adjuvant in the setting of acute postoperative pain,but a new patient-activated electrically facilitated delivery of transdermal fentanyl has been found to be more effective.

Intravenous PCA (patient controlled analgesia)

The factors like pharmacokinetic and pharmacodynamic interindividual variability, break through pain due to inappropriate dose and frequency; can be circumvented to optimize analgesia.This modality is based on the principle of negative feedback.More pain increases demand, which then reduces the pain and next requirement.It is under patient's control.

The side-effects are also reduced, but certain pump malfunctions can be disastrous.The PCA device has the following variables which need to be adjusted before initiating treatment.Demand dose (bolus), lock out interval and the background infusion.

Recommended demand dose for morphine is 1mg and 40 micrograms for fentanyl.

The lockout interval is the safety feature of this pump.The level of analgesia will decrease with too long an interval and side-effects will increase with too short a time by overdose.It is usually kept at 5-10 minutes, depending on the drug formulation being used.The role of background infusion has not found any support in the literature.It can improve analgesia but, can cause cumulation of drug and toxicity.Sleep time background infusion is also not recommended.

The risk of respiratory depression with PCA is <0.5%.This can increase in certain group of patients like; old age, PCA with background infusion, concomitant administration of other hypnotics or sedatives, obstructive sleep apnea, pulmonary disease and ofcourse operator error.

Table(7); Opioid Receptors

Opioid receptors	*μ-1*	*μ-2*	*K*	*Δ*
Effects	Analgesia -supraspinal -spinal Euphoria Low abuse potential Miosis Bradycardia Hypothermia Urine retention	Analgesia -spinal Depression of ventilation Physical dependence Marked constipation Muscle rigidity	Analgesia -supraspinal -spinal Dysphoria Sedation Low abuse potential Miosis Diuresis Psychomimetic	Analgesia -supraspinal -spinal Depression of ventilation Physical dependence Minimal constipation Urinary retention Behavorial epileptogenic
Agonists	Beta-endorphins Morphine Synthetic opioids Met-enkephalins	Beta-endorphins Morphine Synthetic opioids Met-enkephalins	Dynorphins Oxycodone Agonists-antagonists	Leu-enkephalins Beta-endorphins
Antagonists	Naloxone Naltrexone Nalmefene	Naloxone Naltrexone Nalmefene	Naloxone Naltrexone Nalmefene	Naloxone Naltrexone Nalmefene

Sites of opioid activity in the central nervous system:

- **Periaqueductal and periventricular gray**
- **Nucleus reticularis gigantocellularis**
- **Medial thalamus**
- **Mesencephalic reticular formation**
- **Lateral hypothalamus**
- **Raphe nuclei**
- **Spinal cord**
- **Afferent neuron**
- **Periphery**

Administration:

1. Intravenous – 0.1-0.2mg/kg q4-6 hrly (onset-20-30 min, duration-4-6 hrs)
2. Subcutaneous- 0.1-0.4mg/kg 3-4 hrly
3. Intramuscular- same as Subcutaneous
4. Continous infusion -0.01-0.2mg/kg/hr
5. PCA(patient controlled analgesia) bolus 1-3 mg,lockout 5-15 min, no background infusion or 0-1 mg/hr
6. Transdermal patch (synthetic opioids)
7. Oral (for chronic pain)
8. Intrathecal / epidural space- Intrathecal 0.2-0.4mg lasts 4-24hrs,Epidural 2-5mg lasts 4-24hrs
9. Topical cream base (skin grafts)

Monitor for associated side-effects as mentioned in Table(7).

Tramadol

Mechanism

- Centrally acting
- Synthetic opioid
- Weak affinity for μ receptor
- Inhibition of monoamine (norepinephrine and serotonin)reuptake
- Peripheral local anaesthetic properties
- Used for moderate postoperative pain
- 1/10 th as potent as morphine
- Analgesic equivalent to 650mg aspirin, 60mg codeine, 400mg ibuprofen
- Lack of respiratory depression
- No organ toxicity
- Less abuse potential
- Dose- 3mg/kg oral / Intramuscular / Intravenous

Note: High incidence of nausea ,vomiting with Tramadol;

- ❖ Other side-effects are dizziness, sweating, nausea, vomiting, dry mouth and Headache.
- ❖ Caution for use in patients with raised intracranial pressure and history of Seizures.
- ❖ Contraindication in patients on Monoamine oxidase inhibitors.

(ondansetron interferes with analgesia of Tramadol ,since it is due to reuptake inhibition of 5-HT.)

PARACETAMOL/ Acetaminophen

This analgesic effects of this drug was accidently discovered when acetanilide was given to a patient , a decade ago.

It is called as Acetaminophen in the United States and paracetamol in the United Kingdom.

Chemically it is derived from acetanilide and is **N-acetyl-para-aminophenol.**

It is mixed with codeine and marketed as Tylenol.

Manufacturing process:

It is made from phenol, which is combined with nitrate to give ortho and para nitrotoluene.The ortho-nitrotoluene is removed by steam distillation and the other compound para-nitrotoluene is reduced to para-amino group, which is acetylated to yield paracetamol..

Mechanism:

It is a non-steroidal anti-inflammatory drug with Selective inhibition of Cyclooxygenase-3 enzyme in the brain and spinal cord.

This explains its antipyretic action, which is central with lack of anti-inflammatory action peripherally and no unwanted gastrointestinal side-effects.

Dose: Intravenous = 10-15mg/kg q4-6hrly

Suppository = 30-40 mg/kg q4-6hrly

Oral = 250-500mg q4-6hrly or 2-3 g/day

Note: Careful titration of paracetamol in patients with hepatic insufficiency.

Metabolism:

It is broken down in the liver to a quinone compound, which gets conjugated with glutathione to be eliminated from the kidneys.If there is deficiency of glutathione., Quinone accumulates and causes complex formation with liver proteins and nucleic acids.

This toxicity causes Hepatocellular necrosis.The clinical effect manifests after 72-96 hrs.The investigations performed like Liver function tests with values of AST and ALT more than 1000 U/L is diagnostic.

Toxic dose:

Ingestion of 150mg/kg bodyweight or 12gm is toxic in an adult.

Antidotes for paracetamol toxicity:

Methionine and N-acetylcysteine increase the levels of glutathione in the liver, thereby helps to metabolise the toxic compound quinine imine.

Dose of NAC for treating paracetamol overdose is :

150mg/kg in 200ml 5%dextrose over 15minutes

50mg/kg in 500ml 5% dextrose over 4hrs

100mg/kg in 1000ml 5% dextrose over 16 hrs.

Non-Steroidal anti-inflammatory drugs(NSAIDs)

These are non-opioid drugs which have been found to be very effective as adjuncts in moderate to severe pain.They are used alone in treating mild-moderate pain.One of the major mediators of peripheral sensitization and hyperalgesia are prostaglandins.These are synthesized by Arachidonic acid metabolism via a class of enzymes called as cyclooxygenase (COX).NSAIDs , exert their analgesic effect by inhibiting this enzyme.The cyclooxygenase enzyme has also been found in the spinal cord.
There are three isoforms of COX enzyme;

- COX-I : constitutive form
- COX-II: inducible form
- COX- III: central mechanism

Whereas COX I is responsible for platelet aggregration, hemostasis and gastric mucosal protection; COX- II causes pain, inflammation and fever.This profile has prompted the synthesis of selective COX-II inhibitors.Generally NSAIDs are both COX-I and COX-II inhibitors.

The new variant COX-III, includes antipyretics like paracetamol, which decrease pain and fever via specific central mechanism.
These drugs form an integral part of multimodal analgesic techniques.NSAIDs have been found to decrease opioid related side-effects, more than paracetamol.

Their use is not without drawbacks.The side-effects of NSAIDs consumption are bleeding, gastrointestinal hemorrhage, renal dysfunction and deleterious effect on bone growth.

The reason for impaired hemostasis is due to inhibition of COX-I ,which generated thromboxane-A2 , responsible for platelet aggregration and vasoconstriction and also platelet dysfunction.

Renal dysfunction follows NSAIDs consumption, in patients who are hypovolemic, with pre-existing renal failure or abnormal electrolytes.Prostaglandins causes dilation in the renal vascular beds promoting natriuresis.

Gastrointestinal bleeding is due to deficiency of protective gastric mucosal prostaglandins.

Bronchospasm is possible due to cross-sensitivity with aspirin.

All these side-effects can be overcome by using selective COX-II inhibitors.But long term use, has been associated with cardiovascular morbidity.

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Ketamine

This commonly used anaesthetic has analgesic properties at lower doses.It is an N-methyl D-aspartate (NMDA) antagonist.Its mechanism of action involves inhibition of central sensitization.It is very useful in patient's who have developed tolerance to opioids.This low-dose ketamine does not seem to have any hallucinogenic side-effects.

Ketamine is not to be administered neuraxially since its racemic mixture is neurotoxic.

Dosifuser

This is relatively new method of delivering opioid infusion .The pump is based on vaccum .The drug is delivered at a constant pre-fixed rate and cannot be modified.

The manufacturer manual is provided with various drug concentrations along with the dose that will be delivered.

An example is morphine, 60ml of normal saline is mixed with 50mg of morphine, to get a final concentration of 1.3ml/hr = 1mg morphine.

This infusion continues for 2days.

It is very patient friendly, as there is no hindrance to ambulating.

The quality of analgesia achieved is quite satisfactory to most patients.

Newer developments(36)

Capsaicin

TRPV-1 agonist ,non-narcotic acts at C-fibre nerve endings, exhausting stores of substance – P , exhibits opioid-sparing effects.

Pregabalin

It is a structural analog of GABA, has been found to be effective in chronic pain management.

Dexmedetomidine and Clonidine

Both these alpha-2 agonists have opioid-sparing effects.

Tapentadol

This is a new opioid-receptor agonist, with 18 times the affinity as morphine.it inhibits noradrenaline uptake. It is 2-3 times less potent than morphine.

Extended Release Epidural Morphine

Depodur provides pain relief upto 48hrs.

Fentanyl

The Iontophoretic transdermal system creates low-intensity electrical fields across the skin. Its effect lasts for 4 days.

NMDA receptor antagonist

The subanaesthetic doses of Ketamine 0.5-1mg, can inhibit opioid-induced hyperalgesia..

Regional analgesic techniques

These constitute an excellent modality of pain management.An appropriately planned and instituted technique relevant to the surgery, of the patient can almost alleviate postoperative pain.It negates the use of opioids and hence, its side-effects can be avoided.

Single-dose neuraxial opioid

The use of opioids for intrathecal or epidural administration is based on their lipophilicity and hydrophilicity.The drug that is injected intrathecally stays in the cerebrospinal fluid if it is more hydrophilic, like morphine, and then starts acting slowly but effect lasts longer.Morphine moves upwards towards supraspinal area with the CSF flow thus creating more side-effects.Similarly epidurally injected drug slowly migrates into the CSF.

If the drug is more lipophilic it acts fast and is also rapidly cleared from the CSF, hence less adverse-effects.But the duration of analgesic action is short.

Neuraxial morphine effect lasts for 6-24 hrs whereas only 2-4 hrs for fentanyl.

The advantages offered by lipophilic drugs can be utilized in ambulant surgeries.

This duration can be prolonged by adding, 10ml of preservative-free saline to 50-100micrograms of fentanyl.

A new formulation of liposomal encapsulated epidural morphine lasts gives 48hrs of analgesia.

Continous epidural analgesia

An indwelling epidural catheter is a safe and effective method of providing postoperative analgesia.The safety profile is much better as compared to systemic opioids.

Local anaesthetics

The site of action are nerve roots, dorsal root ganglion or spinal cord.It is usual to combine local anaesthetics with an opioid before administration.This improves the quality of pain relief.

Opioids

The use of opioids alone is very useful in patients who cannot tolerate any sympathetic block causing hypotension.It is also used when the site of surgery and catheter placement are not congruent.

Local anaesthetic-opioid combination

The combination of opioid and local anaesthetic can help to decrease the side-effects of each, and at the same time improve the analgesic potency manifold.It prevents regression of sensory block and decreases the dose of local anaesthetic administered. Drugs like bupivacaine <0.125%, ropivacaine <0.2% and levobupivacaine <0.125% are used with fentanyl 2-5 mcg/ml and sufentanil 0.5-1 mcg/ml..

Adjuvants

Clonidine

It acts on the α2 receptors in the spinal dorsal horn,primary afferents, interneurons, descending inhibitory pathway or noradrenergic pathway.The epidural dose is 5-20 mcg/hr.There are side-effects llike bradycardia, sedation and hypotension involved with the use of clonidine..

Epinephrine

This improves the quality of the sensory block, given in doses of 2-5 mcg/ml.

The side-effects with neuraxial opioids are same as the systemic route.

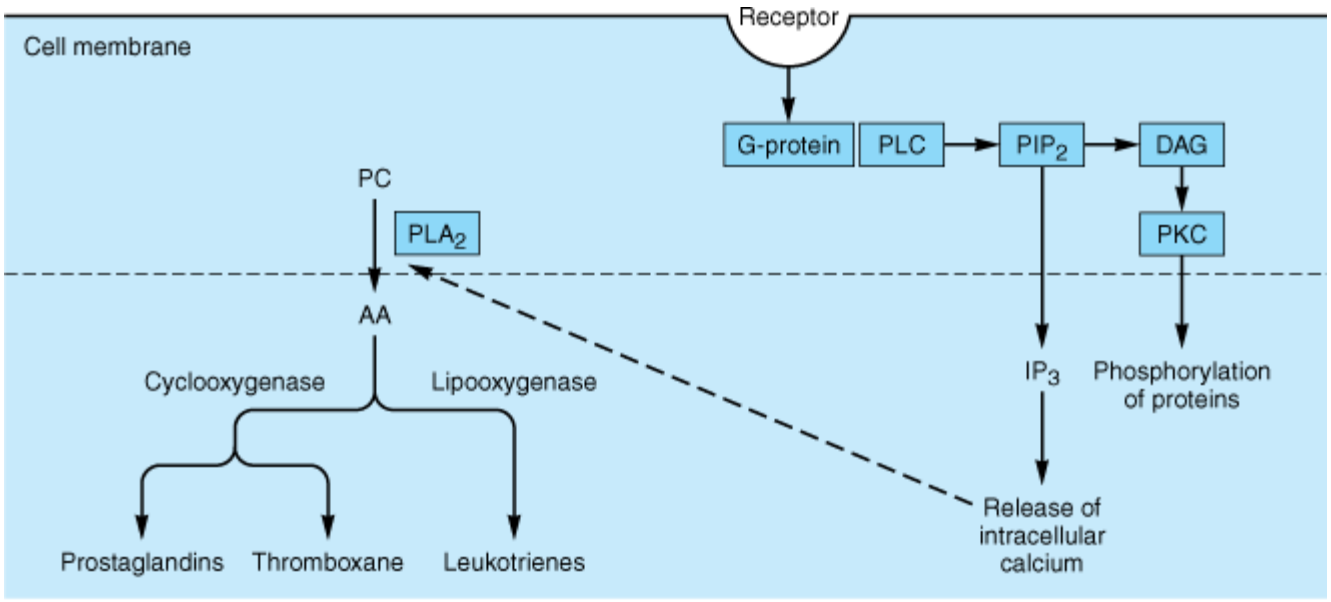
Peripheral regional analgesia

A variety of nerve block techniques, wound infiltration and intraarticular injection can be performed to manage pain effectively.

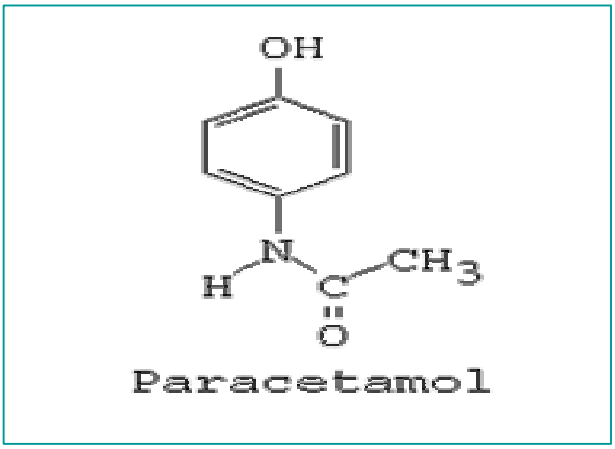
There are many advantages with these methods like; superior analgesia, less side-effects due to opioids or neuraxial techniques.

These procedures are done intraoperatively to continue into the postoperative period as an adjunct.

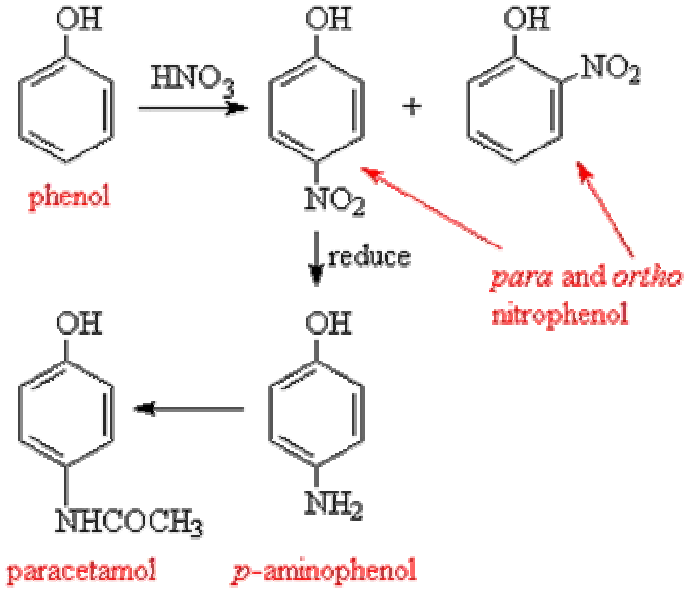
It needs expertise to perform nerve blocks, as they can be associated with complications like nerve injury, hematoma, intravascular instillation of the local anaesthetic.



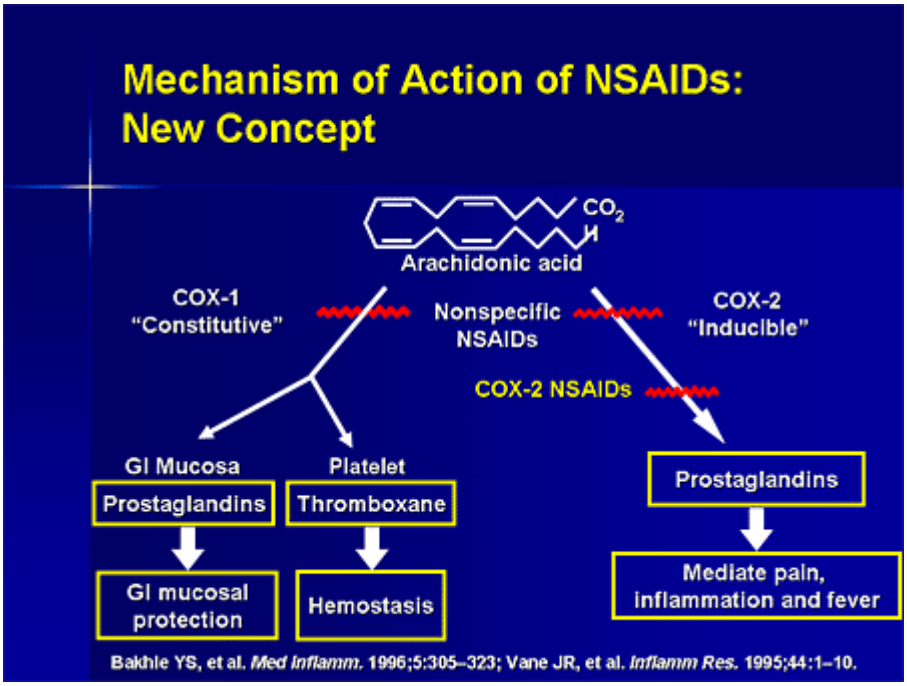
Fig(21); Arachidonic Acid Metabolism



Fig(22); Chemical structure of Paracetamol



Fig(23); Synthesis of Paracetamol



Fig(24); A new model to explain the mechanism of action of Non-Steroidal anti-inflammatory drugs.

T. <u>Non-Pharmacological Techniques of pain management</u>(37)

Assessing a patient's approach to handling any stress, identifies the best suited choice of treatment.

These interventions are Evidence-based adjuncts to somatic modalities.

The most popular of these methods is Acupucture.All these techniques are believed to modify the hypothetical Gate meant to transmit pain signals to higher centres.They improve the functional capacity and activity level of the patient.There is reduction in pain behavior and focused pain levels leading to reduced anxiety and stress levels.Moreover it helps to taper the dosage of analgesics, thus decreasing the unwanted side-effects.

There are four broad categories:

1. Information provision (procedural/sensory)

   The simple description of the procedure to be performed helps in alleviating a major part of fear of it.Patients seem to relax and have a feeling of some control.They know what to expect.

2. Relaxation and Hypnotism (stress reduction)

   These techniques helps in decreasing the sensitivity to pain.It requires the patient to perform breathing excersices like focusing on deep breathing.This also decreases oxygen consumption.It also involves the use of music for the same. There are excercises to relax and contract specific group of muscles to release their tension.The performing of Isometric excercises relieves muscle spasm also.

Hypnotism has been an ancient practice to treat acute pain conditions.It creates an imagery which makes the patient respond to caregiver's suggestions involving changes in perception, memory and voluntary actions.

Evidence from collected data proves that 75% reduction in pain can be achieved.

3. Attention technique

It helps in focussing patient's attention away from the pain, to music, imaged scenes, smells and others.Another method is to make the patient focus on the pain, to attenuate the threat involved.This technique referred to as Meditation, tries to feel pain as other common sensory modalities.It was described by Kabat-Zinn, based on Buddhists teachings.

4. Cognitive intervention

This applies behaviour changing principles like positive reinforcement, modifying thoughts and setting a goal for target behaviour.To establish self-management behaviours and improving self-esteem,this can be applied by all members of the pain team.By keeping a calm and reassuring countenance, it generates support for the patient.

5. Transcutaneous electrical nerve stimulation

   This is for acute, chronic and postoperative pain as an electro-analgesia method.There is modification of the gate control theory.A review on the effectiveness of TENS, did not find any significant improvement.This was attributed to less data for meta-analysis and the intensity being used for stimulation.Bjordal et al in 2003, performed a study by using sub-noxious, non-painful, tolerable intensity with a current amplitude of greater than 15mA.This was found to actually decrease acute pain.High-intensity TENS attenuated pain well.

6. Acupuncture-There is evidence to suggest that the use of this method, relieves postoperative nausea and vomiting.The mechanism is supposed to be the release of endogenous opioids, depending on the frequency of stimulation.Acupuncture inhibits gastric acid secretion and any gastric dysrrhythmia.

7. Manual and Massage therapies

   The manipulation of soft tissues with techniques like percussion, vibration and friction helps to increase threshold of pain.

8. Heat and Cold therapies

   Heat application causes vasodilatation and inhibits the reflex arc.The mode of application is superficial with hot compress and warm baths.Deep application is by using Ultrasound.

   Cold treatment breaks the pain spasm cycle and decreases the transmission in nerve fibres.

9. Acustimulation- This is also called Transcutaneous electrical stimulation.

10. Acupressure- This involves applying pressure at acupuncture points.There are 'True points' and 'Sham points'.Acupressure applied to 'True points' preemptively has shown some benefits.

U. <u>Practice Guidelines for Acute Pain Management in the Perioperative Setting (updated report by the American Society of Anaesthesiologists Task Force on Acute Pain Management; published on October 20,2011)</u>(1)

Salient features of this update are as follows:

A.Institutional policies and procedures for providing perioperative pain management

1.Anaesthesiologists with other health care professionals should provide ,ongoing education and training to hospital personnel.

a) Training should include basic bedside pain assessment to sophisticated pain management techniques like epidural, PCA, regional blocks.

b) Non-Pharmacological techniques like imagery, hypnotism and relaxation.

2. To use standardized, validated tools to periodically evaluate and document pain intensity, effects of treatment and any associated side-effects.

3. Anaesthesiologists should be available 24 hours for any issues related to pain management.

4. Anaesthesiologists assistance regarding any aspect of perioperative pain management should be provide under an Acute Pain Service.

a) There should be healthy participation of anaesthesiologists in framing any standard institutional policies.

B.Preoperative evaluation of the patient

Anaesthetic preoperative assessment should include:

1. Focused pain history

2. Directed physical examination

3. Pain management plan for each patient.

C.Preoperative preparation of the patient

1. To decide which medications should be withheld or continued, to decrease the likelihood oa an abstinence syndrome.

2. Management of preexisting pain.

3. Preemptive initiation of analgesia to control postoperative pain better.

4. Patient and family members should be appropriately educated regarding their roles in providing comfort, reporting pain, and about proper use of relevant analgesic methods for their patient.

5.Misconceptions regarding analgesia, related to adverse effects should be dispelled.

6. Patient should be educated about proper use of patient-controlled analgesic techniques and other therapeutic options, with instructions in behavorial modalities included. This can be aided by the use of brochures, videotapes, and followed up at postoperative bedside visits.

D. Perioperative techniques for pain management

1. The therapeutic options should include epidural or intrathecal opioids , systemic opioid PCA and regional blocks.

a) The above mentioned methos should be used in preferenece to “as needed” intramuscular opioids.

2.The therapy prescribed should reflect individual anaesthetist capacity or ability to manage any adverse effect following treatment.

3. Continous infusions need special attention as drug accumulation leads to inadvertent adverse effects.

E. Multimodal techniques for pain management

1.Anaesthesiologists should follow multimodal analgesia.

2.Around-the-clock regimen of NSAIDs, COXIBs, or Acetaminophen should be prescribed unless contraindicated.

3.Regional techniques should be advocated.

4.Drug dosing should be of optimized efficacy and minimized risks.

5.There should be individualized regimens for medications, dosing,route of administration and duration of therapy.

F.Patient sub-populations

1.Paediatric patients

a) Children need as aggressive pain management as adults.their pain is generally undertreated.

b) They need pain assessment and treatment as appropriate for their development.

c) Pain therapy should be based on age, weight, and any comorbidity.

d) A multimodal approach should be followed.

e) Behavorial techniques for the emotional component of pain is to be applied whenever possible.

f) For any painful procedure sedatives, analgesics and local anaesthetics should be used with appropriate monitoring.

2. Geriatric patients

a) Pain Assessment Tools should be chosen depending on patient's cognitive abilities.

b) To overcome barriers limiting the proper reporting of pain, an extensive questioning may be required.

c) The Co-morbidities of any geriatric patient should be kept in mind while formulating analgesic plans.

3. Other Subpopulations

Additional interventions would be required in the following subgroups:

a) Critically ill patients

b) Cognitively impaired

c) Communication difficulties

4.After excluding other causes of pain, in a patient with elevated heart rate and blood pressure or agitation; anaesthetists should take the patient through a therapeutic trial of an analgesic protocol.

V. <u>A brief note on chronic pain</u>:

Pain of any etiology lasting for 3 – 6 months is referred to as chronic pain.

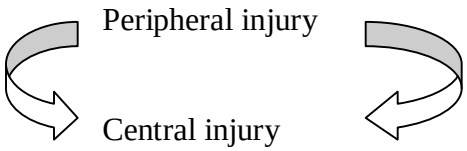
Pathophysiology of chronic pain

Undertreated acute pain progresses to chronic pain

<u>Mechanism</u>:

Tissue injury and Inflammation

Peripheral and Central Sensitization



Modification of Neuroplasticity

Uncontrolled Sensitization progresses to chronic pain

Justification

A review of Literature reflects multiple aspects of acute pain, the knowledge of this dimension is of paramount importance, in enhancing the quality of our patient's lives.An Audit is one such standardized tool, that helps to gauge our current level of knowledge and patient care.We want to evaluate the effectiveness of our practices concerning acute pain management.

Research questions

1. Is the postoperative Analgesia adequate? Are our patients satisfied with their pain management?
2. Is the Universal Pain Assessment Tool, being used effectively?
3. What is the scope of introducing services pertaining to a Pain nurse or Nurse-based Anaesthetist supervised Acute pain services ?

METHODOLOGY

Brief summary of the study

This study is an observational audit, to assess the adequacy of acute pain relief, in our postoperative patients.The proposal was discussed by the research and ethics committee, and was approved upon.

This observational study included all gynecology inpatients undergoing any open abdominal procedure ,with normal mental health and hospitalized for atleast 48hrs postoperatively.We audited 200 inpatients, ASA grade I-III, with ward follow-ups.A written informed consent, was duly explained and obtained from all patients on the pre-operative day.

There were no modifications done in the pre-operative medications whatsoever.

After the surgery these patients were followed up for 48hrs, in the ward intermittently.the data collected is mentioned in the data sheet in the Appendix.

It broadly involves demographics, ASA grade, pain scores on day1 and 2, medication details and side-effects.The audit ended here.

Methodology in Detail

Study design:

An Observational Study.

Intervention:

Nil

Study Setting and Population:

This audit was conducted on inpatients in the Gynecology wards admitted for major surgery.The permission to conduct an audit was obtained from the Department of Obstetrics and Gynecology.

Key Criteria

Inclusion Criteria:

All obstetrics-gynecology inpatients undergoing any open abdominal procedure,with normal mental health and hospitalized for atleast 48 hrs postoperatively.

Exclusion Criteria:

Our exclusion criteria includes all patients transferred directly to an Intensive Care Unit,those who had Emergency procedure or discharged in less than 48hrs.

PRIMARY OBJECTIVE:

Assessment of Adequacy of current analgesic protocols.

SECONDARY AIMS:

a)Assessing the need of a pain nurse in our setting.

b)To establish the necessity of a functioning Acute Pain Service in Obstetrics-Gynecology Department.

Target Sample Size and Rationale

The sample size was calculated after a review of various articles related to this audit.

It was found that the incidence of moderate to severe pain postoperatively was 40-60%.

Sample Size Calculation Formula

Estimation of Single Proportion
Formula

$$n = \frac{Z^2_{1-\alpha/2}\, p(1-p)}{d^2}$$

Where,

p : Expected proportion

d : Absolute precision

1- α/2 : Desired Confidence level

Audit Period

6 months

Statistical Analysis

The outcome of the audit is derived by using frequency tables.

It also estimates valid percent and cumulative percent.

Measurements

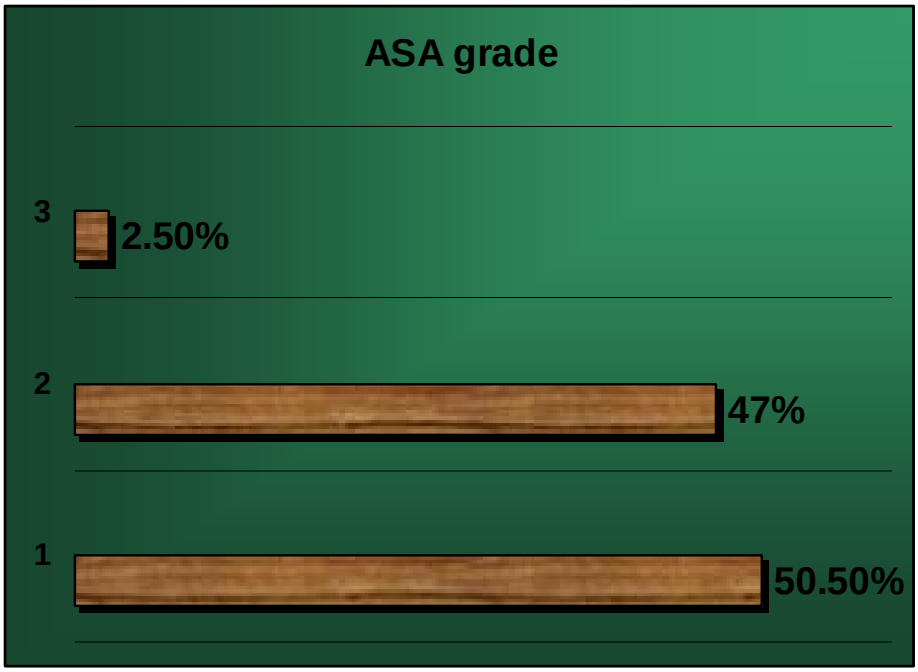
RESULTS

The software used for data management is the **Epidata version 3.1**.

Total patients screened 200.

All are female patients with age distribution from 16 – 60 years .

1) ASA grade



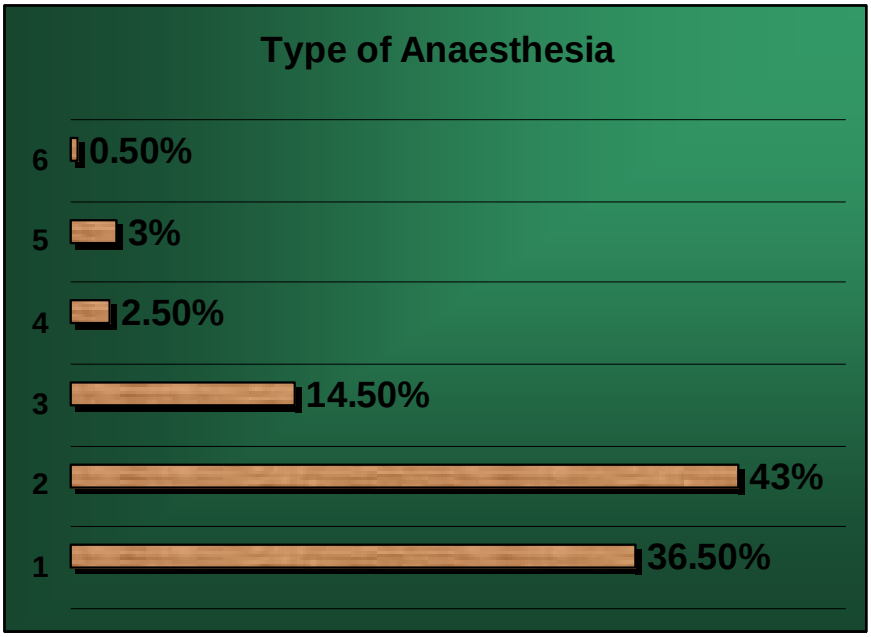
Fig(25);The above pie chart depicts the relative percentages of patients in various ASA categories, in this audit.

As evident above 50% patients belonged to ASA grade I,

47% were ASA grade II and 2.5% ASA grade III.

(ASA-American Society Of Anaesthesiologists)

2) TYPE OF ANAESTHESIA



Fig(26);As shown above ,the type of Anaesthesia received varied between the aforementioned categories.

1-General Anaesthesia,

2 -Subarachnoid block

3 -General Anaesthesia with Epidural

4 -Combined Spinal Epidural

5 -Subarachnoid block converted to General Anaesthesia

6 -Laryngeal Mask Airway with Epidural.

Most of our patients received a Spinal Anaesthesia, closely followed by General Anaesthesia technique.

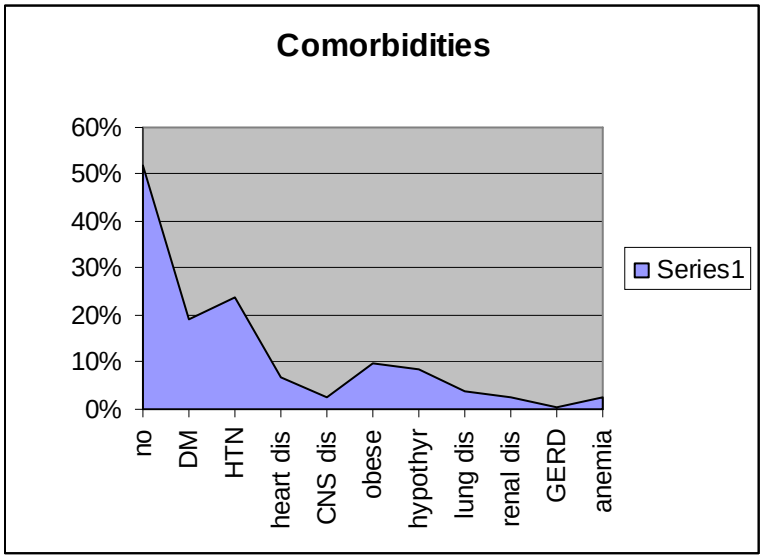
3) Type Of Surgery

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	78	39.0	39.0	39.0
	2	35	17.5	17.5	56.5
	3	32	16.0	16.0	72.5
	4	27	13.5	13.5	86.0
	5	10	5.0	5.0	91.0
	6	1	.5	.5	91.5
	7	2	1.0	1.0	92.5
	8	2	1.0	1.0	93.5
	9	1	.5	.5	94.0
	12	1	.5	.5	94.5
	13	3	1.5	1.5	96.0
	14	1	.5	.5	96.5
	15	3	1.5	1.5	98.0
	16	2	1.0	1.0	99.0
	17	1	.5	.5	99.5
	18	1	.5	.5	100.0
	Total	200	100.0	100.0	

Fig(27);1.Total abdominal hysterectomy
2.Vaginal hysterectomy
3.Lap Assisted vaginal hysterectomy
4.Staging laparotomy
5.Myomectomy
6.Sacrospinous hystereopexy
7.Interval debulking
8.Septal resection
9.Laparoscopy for endometriosis
10.Laparoscopy for rudimentary horn excision
11.Perineal mass excision
12.Wide local excision and Bilateral inguinofemoral lymphadenectomy
13.Prolapse repair
14.Laparoscopy converted to open
15.Vaginoplasty
16.Resuturing
17.Radical vulvectomy18.Conisation

About 39% of patients underwent Total abdominal hysterectomy, with an almost equal distribution among those who had undergone vaginal hysterectomy, lap assisted vaginal hysterectomy and staging laparotomy.while the remaining surgeries were few and varied.

4) Co-Morbidities



Fig(28);This graph shows the incidence of Co-Morbidities in this Audit .

As evident from the graph, Diabetes and Hypertension were more common, closely followed by patients with hypothyroidism and obesity.

5) Pain Scores

The codes for this category are listed as follows:

0.No pain

1.No pain to Mild pain

2.Mild pain

3.Mild pain to Moderate pain (interferes with tasks)

4.Moderate pain (interferes with tasks)

5.Moderate pain (interferes with tasks) to moderate pain (interferes with concentration)

6.Moderate pain (interferes with concentration)

7.Moderate pain (interferes with concentration) to severe pain

8.Severe pain

9.Severe pain to worst pain possible

10.Worst pain possible

***The criteria for this audit is a pain score of 3, mild pain to moderate pain (interferes with tasks) and > 3.**

DAY 1 Max Pain Scores

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	14	7.0	7.0	7.0
	2	52	26.0	26.0	33.0
	3	56	28.0	28.0	61.0
	4	57	28.5	28.5	89.5
	5	14	7.0	7.0	96.5
	6	5	2.5	2.5	99.0
	7	1	.5	.5	99.5
	8	1	.5	.5	100.0
	Total	200	100.0	100.0	

Table(8);These are the maximum pain scores on the first Post operative day.

There are 67% of patients who had significant pain on Day 1.

(Significant pain for this audit is score 3 & >3)

DAY 2 Max Pain Scores

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	16	8.0	8.0	8.0
	2	94	47.0	47.0	55.0
	3	43	21.5	21.5	76.5
	4	39	19.5	19.5	96.0
	5	4	2.0	2.0	98.0
	6	4	2.0	2.0	100.0
	Total	200	100.0	100.0	

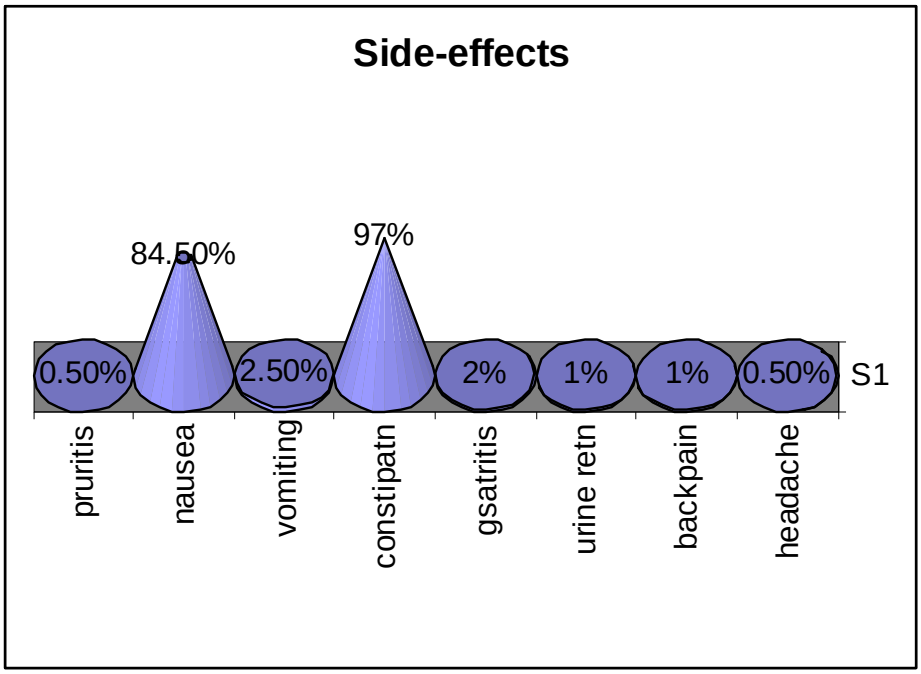
Table(9);These are the maximum pain scores on the Second post operative day. There are 45% of patients who had significant pain on Day 2. (Significant pain for this audit is score 3 & >3)

4.MEDICATIONS

Medication	*Day1(received by patients)*	*Day2(received by patients)*
Morphine	42% (25.5%-subcutaneous q6h)	41% (18.5%-subsctaneous prn)
Tramadol	49% (38.5%intramuscularq6h)	63% (33.5% intramuscularq6h)
Epidural infusion	16.5%	15%
Dosifuser morphine	2%	1.5%
Febrinil	59%(26.5%intravenousq8h)	56%(23%intravenousq8h)
Aknil	15.5% - intramuscular prn	14.5% -intramuscular prn
Perfalgan	17.5%(11%intravenousq6h)	18%(11%intravenousq6h)
Metacin	4% - per oral prn	40%(33.5%per oral prn)
Ketonov	10%(4%intramuscularq8h)	26%(23%per oral q8h)
Voveran	10%(9% - patch od)	17.5%(17% - patch od)
Proxyvon	2%- per oral tid	14%(12.5%- per oral tid)
Emeset	91%(45%-intravenousq8h)	89.5%(25.5%-per oral tid)
Phenergan	47%(37%intramuscularq6h)	49.5%(33.5%intramuscularq6h)
Ranitidine	39.5%(30.5%intravenousq8h)	43%(25%- per oral q12h)
Pantoprazole	40%(38.5%-intravenous od)	41.5%(22.55-per oral od)

Table(10);The percentages of various drugs administered for pain

6) SIDE-EFFECTS



Fig(29);Various side-effects developed Post-operatively.

Here constipation closely followed by nausea, were the most common problems encountered by patients.

Table(11);Percentage of Intramuscular Injections

Medication	*Route*	*Day 1*	*Day 2*
Tramadol	**Intramuscular**	**47.5%**	**47.5%**
Aknil	**Intramuscular**	**15.5%**	**14.5%**
Ketonov	**Intramuscular**	**7%**	**3%**
Phenergan	**Intramuscular**	**45%**	**47.5%**

The trend towards prescribing frequent intramuscular injection is seen from these figures.

Table(12);DAY 1 Pain Scores / Analgesics

Pain score	No.of patients	Morphine	Tramadol	Epidural	Morphine & epidural	Tramadol & epidural	Dosifuser
3	55	20	26	3	5	1	-
4	57	25	29	1	1	1	-
5	13	6	5	-	1	-	-
6	5	1	1	2	-	-	1
7	1	1	-	-	-	-	-
8	1	-	1	-	-	-	-
Total	132						

Table(13);DAY 2 Pain Scores / Analgesics

Pain acore	No.of patients	Morphine	Tramadol	Epidural	Morphine & epidural	Tramadol & epidural	Dosifuser
3	41	15	18	3	4	-	-
4	39	22	14	1	-	1	-
5	4	3	1	-	-	-	-
6	4	2	2	-	-	-	-
7	-	-	-	-	-	-	-
8	-	-	-	-	-	-	-
Total	88						

The above tabulated data is reflecting the pain scores with the kind of analgesia received.There is no comparison between scores, as it is a subjective entity.

DISCUSSION

This audit was conducted in the Obstetric and Gynecology Department, of Christian Medical College Hospital in Vellore; Tamil nadu. This hospital has 2,695 beds,and caters to 5500 outpatients, 2500 inpatients per day, functioning at a tertiary care level.There is a rapid turnover of patients, who undergo surgical procedures.On an average, 100 surgeries and 25 procedures are performed everyday in the 35 operation theatres.A large sum of the hospital revenue depends on the working of the operation theatres.We had set out to do an audit on postoperative patients ,to assess the adequacy of their acute pain relief.We wanted to generate a feedback, for all the modalities concerning pain.It is basically a survey to assess our current practices of pain treatment, to lay the groundwork for future modifications.The postoperative orders vary a lot within the multiple units shared by each speciality.For initiating such Audits in all the departments of our hospital, we started with the Obstetrics and Gynecology speciality.We have a functioning Acute Pain Service, but its involvement in the OBG wards is nearly negligible.Our institute and its infrastructure, provides a wide population with all its patients and healthcare professionals, to create a strong self-sufficient pain management cell. There is a need to have such an establishment for the whole hospital to rely and fall back upon.A Painometer has been established in all our wards.This is because pain is not assessed like other vital parametersProgrammes like training, education, research on newer modalities of pain relief and their implementation,a 24hrs availability of pain specialist to clarify and seek help with managing any patients pain, should form an integral part of this system.A review of articles related to this concept revealed numerous studies done around similar objectives.

An intervention study for improving postoperative pain management by introducing APS was done by Francoise(38) et al, in the University Hospital, Belgium.there was significant improvement noticed in pain scores with P value < 0.001. Every patient is different and same protocols may not work for all patients.Rescue analgesics are mandatory in the face of such diversity, to relieve break-through pain anytime.As Pam McIntyre said “No pain therapy is a one glove fits all”thrapy, postoperative therapies are only maintenance therapies.

The 1997 recommendations by the UK Audit Commission(39), suggest a target with <20% patients in severe pain, to fall to <5% by 2002.What are all these programmes aiming at? The answer is very simple, if you ask a patient in pain;pain-free hours at rest, on movement and a good nights sleep.The hospitals in developed countries are assessed on the merits of pain relief that they achieve, there are still many barriers to reach such standards in the developing world.There are still those among us who think ‘its all in the mind’.The value of clinical Audit on pain management was seen in one study done at the University of Wales (40) College of Medicine, where an overall reduction in patients experiencing pain was observed.Another audit covering a vast percentage of patients, conducted in United Kingdom(41), resulted in data suggesting 60% patients with unacceptable pain 24hrs postoperatively.In this study most women underwent hysterectomies, got a PCA and had the highest pain scores.At the Queen Mary Hospital, Hongkong(42), an audit on Chinese patients, found epidural and PCA very effective.The incidence and severity of postoperative pain, especially severe pain was 46.4% , in an audit of surgery clinics in Paris(43).

From 1973-1999, a MEDLINE (39)search and review reveals a significant reduction in moderate to severe pain;P value <0.001, of 1.9% annually.But the current protocols are inadequate to achieve set recommendations.There is fear of excellent analgesics like morphine, which leads to underprescription and prn orders.India is one of the major exporters of morphine, but the consumption is very low.

The concept of Nurse-based, Anaesthetist-supervised Acute Pain Service(44); gains more importance as there is a surge in the use of applications like epidurals, PCA, dosifusres for alleviating pain.These are very patient friendly, but need well informed personnel to manage.The introduction of a specialist pain nurse(45)(46), enhances the safety profile of these sophisticated techniques.Such a network of healthcare professionals with a vision to eradicate pain, would need standardized tools like Audits on a periodic basis.As “Pain knowledge is not to know, but to do;” we need to keep working at progressing on this quest for, bringing about new radical changes.We at Christian Medical College Hospital, Vellore are trying to develop a dedicated unit for pain management.This would consist of a Section Anaesthesiologist, pain representative from each department;with a meeting every 3 months.The norm “APS not a one man show-definitely a team approach’, applies well.

Discussion on the Results of this Audit

This Audit was done on all female patients from the age group of 16 to 60 years of age.Their categorization into ASA grades was, about 50.5% of ASA grade I, 47% of ASA grade II, and 2.5% were of ASA grade III.About 39% patients underwent Total Abdominal Hysterectony.The type of Anaesthesia mostly used was spinal anaesthesia, in 43% patients.The commonly performed surgeries seemed to be Total Abdominal Hysterectomy, Vaginal Hysterectomy, Lap-assisted Vaginal Hysterectomy, and Staging Laparotomy.

Among our patients, Co-morbidities like Diabetes, Hypertension, hypothyroidism, and Obesity seemed more prevalent.After analyzing the pain scores, we found that about 67% patients were in significant pain on the first postoperative Day, and 45% on the second postoperative Day.

A review of their prescriptions was done and Tramadol based analgesic protocol was found in 49% doctor order sheets, on first postoperative day and 63% on second postoperative day.These were mostly administered by intramuscular route.Morhine based treatment was received by 42% patients on the first postoperative day and 41% on second postoperarive day.The commonly followed route for Morphine was subcutaneous.Only 15-16% patients had received the benefit of an Epidural.The Epidural infusion was continued for a maximum of 48hrs and discontinued.This infusion was being stopped whenever the patient was ambulant.Any complication like hypotension was supposed to be due to Epidural infusion. Some feedback from the nurses suggested that, they did not get adequate support from our existing personnel involved with pain services.

Dosifuser usuage was done in only 2% patients.One such infusion was discontinued due to lack of knowledge about the modality.All the protocols followed were based on a Multimodal approach, but the dosages were inadequate and frequency of administration variable.Several combination of paracetamol, voveran, proxyvon, ketonov with emeset, phenergan, ranitidine ans pantoprazole were noticed.The brand of paracetamol frequently used was Febrinil.

The most common side-effect was constipation, followed by nausea.

Ambulation was started on Day II.

This concludes the results.

Conclusion

PRIMARY OBJECTIVE: Assessment of adequacy of current analgesic protocols.

According to this audit, the analgesic protocols being followed are inadequate and non-uniform.

SECONDARY AIMS: a)Assessing the need of a pain nurse in our setting.

Pain management and care are very focused specialities, especially in such a huge set-up.

The inclusion of trained pain nurses is necessary to train other nurses in the ward.

b) To establish the necessity of a functioning Acute Pain Service in Obstetrics-Gynecology Department.

A dedicated Acute Pain Service will be very beneficial in the Obstertrics and Gynecology Department.

Limitations

Pain is usually pronounced as a very subjective experience,

Pain scores are done by nurses, so their knowledge regarding the audit tool is a limitation for accuracy.

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APPENDIX – 1

Data collection sheet

DATA SHEET

1.PATIENT DEMOGRAPHICS
Patient name -
Hospital number(as per inpatient record) -
Age (yrs) -

2.SURGICAL INFORMATION
Surgical procedure(elective)-

3.MEDICAL /PAIN HISTORY
Comorbidities-
Pre-existing pain-
Regular analgesic use-
Allergies-

4.ANAESTHETIC INDICES
Height (cms)-
Weight(kgs)-
ASA grade(I-VI)-
Type of anaesthesia –

5.POSTOP PAIN MANAGEMENT VARIABLES
Pain assessment tool – universal pain assessment tool
Patient observations recorded during the audit period
Audit period chosen – postop 48hrs
Highest pain score documented during the audit period-DAY 1 =
DAY 2 =
6.patient postop analgesia during the audit period

ANALGESICS prescribed & administered during the audit period

ANALGESICS (generic)	**DAY 1**	**DAY 2**	**ROUTE**	**FREQUENCY**

ADJUVANTS:

MEDICATION (generic)	Day 1	Day 2	ROUTE	FREQUENCY

Postoperative problems related to medications administered

SIDE-EFFECTS	DAY 1	DAY 2	FREQUENCY
None Pruritis Nausea Vomiting Constipation Gastritis Loss of appetite Drowsiness Urine retention Back pain			
headache			

Ambulation started when-
Frequency of intravenous cannulation / removal-
Epidural infusion continued on DAY1=
DAY2=
Dosifuser continued on DAY1=
DAY2=

APPENDIX – 2

Data code-sheet

v1 ID <IDNUM>

v2 NAME _____

v3 HOSPITAL NUMBER ######<A>

v4 AGE(yrs) ##

v5 GENDER # 1.female

v6 HEIGHT(cms) ###

v7 WEIGHT(kg) ###

v8 ASA GRADE # 1.a normal healthy patient.
2.patient with mild systemic disease.
3.patient with severe systemic disease.
4.patient with severe systemic disease that is a constant threat to life.
5.a moribund patient who is not expected to survive Without the operation.
6.a declared brain dead patient whose organs are being harvested for donor purposes.

v9 TYPE OF ANAESTHESIA # 1.general anaesthesia
2.spinal anaesthesia
3.general anaesthesia with epidural block
4.combined spinal epidural
v10 5.spinal converted to general anaesthesia #
1.patchy/pain
2.inadequate surgical relaxation
6.GA with LMA and epidural

v11 TYPE OF SURGERY ## 1.Total abdominal hysterectomy
2.Vaginal hysterectomy
3.lap assisted vaginal hysterectomy
4.staging laparotomy
5.myomectomy
6.sacrospinous hystereopexy
7.interval debulking
8.septal resection
9.laparoscopy for endometriosis
10.laparoscopy for rudimentary horn excision
11.perineal mass excision
12.Wide local excision and bilateral inguinofemoral lymphadenectomy
13.prolapse repair
14.laparoscopy converted to open
15.vaginoplasty
16.resuturing
17.radical vulvectomy
18.conisation

```
v12  no comorbidities
v13  diabetes melitus <Y>
v14  hypertension <Y>
v15  heart disease <Y>
v16  CNS disease <Y>
v17  obesity <Y>
v18  hypothyroidism <Y>
v19  lung disease <Y>
v20  renal disease <Y>
v21  gastroesophageal reflux disease <Y>
v22  tuberculosis <Y>
v23  spinal cord pathology <Y>
v24  neuromuscular pathology <Y>
v25  anemia <Y>


v26   PRE-EXISTING PAIN  <Y>

v27   REGULAR ANALGESIC USE <Y>

v28   ALLERGIES _________________

v29   HIGHEST PAIN SCORE DAY 1 # 0.no pain
                        DAY 2 # 1.no pain to mild pain
                                2.mild pain
                              3.mild pain to moderate pain(interferes with tasks)
                              4.moderate pain (interferes with tasks)
                              5.moderate pain (interferes with tasks) to
                                moderate pain (interferes with concentration)
                              6.moderate pain (interferes with concentration)
                              7.moderate pain (interferes with concentration)
                                to severe pain
                              8.severe pain
                              9.severe pain to worst pain possible
                             10.worst pain possible

v30  ANALGESIC ADMINSTERED  morphine DAY 1 ##  0.none
v31                                 DAY 2 ##  1.morphine intravenous q6
                                              2.morphine intravenous q4h
                                              3.morphine subcutaneous q6h
                                              4.morphine subcutaneous q4h
                                              5.morphine subcutaneous prn
                                              6.morphine intrathecal
                                              7.morphine infusion (dosifuser)
                                              8.morphine PCA
                                              9.morphine subcutaneous q8h
                                             10.morphine intravenous q8h


v32                             tramadol DAY 1 # 0.none
v33                                      DAY 2 # 1.tramadol intramuscular q8h
                                                 2.tramadol intramuscular q6h
                                                 3.tramadol intramuscular prn
                                                 4.tramadol per oral q12h
                                                 5.tramadol intravenous q8h
                                                 6.tramadol per oral q8h
                                                 7.tramadol intravenous q6h

v34                             pethidine DAY 1 #         0.none
v35                                       DAY 2 #         1.pethidine


v36                             febrinil DAY 1 #    0.none
```

```
v37                                    DAY 2 #    1.febrinil intravenous q8h
                                                  2.febrinil intravenous q6h
                                                  3.febrinil intravenous prn
                                                  4.febrinil intravenous od

v38                            aknil    DAY 1 #   0.none
v39                                     DAY 2 #   1.aknil intramuscular prn


v40                            perfalgan DAY 1 #  0.none
v41                                       DAY 2 #  1.perfalgan intravenous q6h
                                                  2.perfalgan intravenous q8h
                                                  3.perfalgan intravenous prn

v42                            metacin DAY 1 #    0.none
v43                                    DAY 2 #    1.metacin per oral prn
                                                  2.metacin per oral q8h
                                                  3.metacin per oral q6h




v44                            ketonov DAY 1 #    0.none
v45                                    DAY 2 #    1.ketonov intramuscular prn
                                                  2.ketonov intramuscular q8h
                                                  3.ketonov per oral q8h
                                                  4.ketonov per oral prn



v46                            voveran DAY 1 #    0.none
v47                                    DAY 2 #    1.voveran patch once daily
                                                  2.voveran intravenous prn
                                                  3.voveran suppository pr bd

v48                            proxyvon DAY 1 #   0.none
v49                                     DAY 2 #   1.cap.Proxyvon po tid
                                                  2.cap.proxyvon po bd



v50   ANTI-EMETICS emeset DAY1 #            0.none
v51                       DAY 2 #          1.emeset intravenous q6h
                                           2.emeset intravenous q8h
                                           3.emeset intravenous prn
                                           4.emeset per oral tid
                                           5.emeset intravenous bd
                                           6.emeset per oral prn
                                           7.emeset subcutaneous tid



v52                  phenergan DAY 1 #     0.none
v53                            DAY 2 #     1.phenergan intravenous q12h
                                           2.phenergan intravenous q8h
                                           3.phenergan intramuscular prn
                                           4.phenergan intramuscular q6h
                                           5.phenergan intramuscular q8h
                                           6.phenergan intravenous q6h
```

```
v54   ACID PROPHYLAXIS ranitidine DAY1 #     0.none
v55                              DAY 2 #    1.ranitidine intravenous q8h
                                            2.ranitidine per oral q12h
                                            3.ranitidine intravenous q12h
                                            4.ranitidine intravenous prn
                                            5.ranitidine per oral q8h


v56                  pantoprazole DAY 1 # 0.none
v57                               DAY 2 # 1.pantoprazole intravenous once daily
                                            2.pantoprazole per oral once daily
                                            3.pantoprazole intravenous bd
                                            4.pantoprazole intravenous prn


   SIDE-EFFECTS
v58     none <Y>
v59     pruritis <Y>
v60     nausea <Y>
v61     vomiting <Y>
v62     constipation <Y>
v63     gastritis <Y>
v64     loss of appetite(LOA) <Y>
v65     drowsiness <Y>
v66     urine retention <Y>
v67     back pain <Y>
v68     headache <Y>


v69   EPIDURAL CATHETER INSERTED <Y>

v70  EPIDURAL CATHETER ACCIDENTAL REMOVAL IN OR <Y>

v71   EPIDURAL INFUSION DAY1 <Y>
v72                      DAY2 <Y>

v73   EPIDURAL INFUSION STOPPED AND RESTARTED <Y>

v74   EPIDURAL INFUSION RATE ALTERED <Y>

v75   AMBULATION STARTED DAY #

v76   FREQUENCY OF INTRAVENOUS CANNULATION #

v77  DOSIFUSER DISCONTINUED ON  DAY 1 <Y>
v78                             DAY 2 <Y>
```

APPENDIX – 3

Data Entry Spreadsheet

ID no	HOSPI NO	AGE	GENDER	HTcms	WTkg	ASA gd	ANAES	SA to GA
1	585030D	59	1	165	55	2	4	
2	169168F	46	1	155	45	1	1	
3	457889D	40	1	160	65	1	1	
4	251389F	54	1	160	50	1	1	
5	281245D	56	1	160	50	3	1	
6	225082F	39	1	155	53	1	3	
7	82387F	40	1	165	65	1	1	
8	217772F	24	1	165	65	1	2	
9	226550F	28	1	145	46	1	3	
10	235231F	40	1	164	62	1	2	
11	428431B	38	1	154	69	2	2	
12	252391C	46	1	150	60	1	2	
13	187308B	58	1	150	49	1	5	1
14	255327F	48	1	155	45	1	2	
15	22665F	51	1	160	74	1	2	
16	971560B	62	1	144	60	3	1	
17	168502F	43	1	155	51	1	2	
18	604737A	48	1	160	55	2	2	
19	216400F	73	1	160	80	2	2	
20	228651F	47	1	160	63	1	2	
21	249831F	52	1	160	68	2	1	
22	826837D	48	1	155	46	1	2	
23	284956F	22	1	155	53	1	3	
24	83354C	57	1	150	68	2	1	
25	266571F	48	1	160	68	1	2	
26	276287F	65	1	155	40	1	4	
27	274134F	40	1	165	56	2	1	
28	958098A	46	1	155	65	1	1	
29	253392F	55	1	150	60	2	2	
30	188598F	49	1	160	65	2	2	
31	210578F	50	1	150	37	1	2	
32	232938F	57	1	165	54	2	3	
33	263270F	62	1	165	54	1	1	
34	253617D	48	1	160	81	2	3	
35	305608B	33	1	155	75	1	1	
36	872328D	46	1	155	86	2	1	
37	282307F	50	1	155	50	1	2	
38	217150F	50	1	160	70	1	5	2
39	35765F	42	1	160	59	2	2	
40	282876F	57	1	150	59	2	1	
41	402209C	55	1	150	79	2	2	
42	385990B	51	1	167	60	2	1	
43	193975D	56	1	150	45	2	2	
44	533683D	41	1	156	64	2	1	
45	27330F	39	1	150	65	1	3	
46	110218C	50	1	159	60	2	6	
47	411245D	38	1	157	74	2	2	
48	192950F	16	1	165	74	2	5	2
49	416674D	48	1	165	71	2	1	
50	659171D	44	1	165	65	1	1	
51	179864F	43	1	159	91	2	1	

52	124940D	55	1	156	72	2	2	
53	163789F	65	1	155	71	2	3	
54	176572F	18	1	168	60	1	1	
55	467940B	58	1	158	48	2	2	
56	146773F	50	1	150	40	1	5	1
57	197045F	45	1	162	48	1	2	
58	169558F	42	1	155	68	1	2	
59	172642F	46	1	160	66	2	2	
60	73592F	57	1	158	58	2	2	
61	177131F	58	1	155	44	2	5	1
62	649644D	51	1	155	45	1	2	
63	820889D	53	1	156	88	2	1	
64	96765F	38	1	155	62	1	1	
65	774655D	46	1	165	65	1	1	
66	476019D	43	1	160	50	1	2	
67	164702F	60	1	155	52	2	3	
68	921875B	34	1	165	65	1	2	
69	140072F	25	1	160	50	1	2	
70	903728D	21	1	160	80	2	2	
71	187667	36	1	155	60	1	2	
72	121922	40	1	155	70	1	2	
73	949858D	53	1	155	60	1	2	
74	260683D	31	1	155	53	1	2	
75	58350F	45	1	154	60	1	1	
76	95754F	38	1	165	60	1	1	
77	176712F	54	1	175	103	3	5	1
78	98350B	53	1	155	77	2	1	
79	126815C	39	1	155	60	1	2	
80	138578D	60	1	150	60	3	1	
81	23078F	36	1	145	46	1	2	
82	279828F	14	1	140	34	1	1	
83	118506C	55	1	160	60	2	1	
84	276100F	11	1	133	37	1	1	
85	284356F	15	1	145	50	2	2	
86	270648F	30	1	165	85	2	3	
87	236550F	40	1	165	65	2	3	
88	248209F	37	1	140	67	2	3	5
89	62129C	48	1	165	75	2	1	
90	517911C	48	1	155	62	1	1	
91	260533A	65	1	160	65	2	2	
92	93479F	44	1	175	95	2	1	
93	704096A	53	1	155	50	2	2	
94	279071F	48	1	155	51	2	1	
95	251303F	24	1	165	45	1	4	
96	873403D	46	1	156	54	1	2	
97	740299B	55	1	165	65	1	4	
98	253029F	53	1	150	57	2	3	
99	281307F	42	1	165	65	1	1	
100	221165F	49	1	165	55	3	3	
101	263081F	70	1	155	39	2	2	
102	839468D	43	1	170	75	2	1	
103	197075F	21	1	155	40	1	1	

104	268523F	15	1	150	50	1	3
105	266124F	48	1	150	50	1	2
106	53353F	41	1	160	64	2	2
107	357741D	40	1	146	64	1	2
108	976034D	41	1	152	64	1	1
109	239616F	40	1	170	60	1	1
110	277471F	39	1	150	48	1	1
111	293581F	75	1	148	41	1	2
112	231758F	47	1	150	47	1	2
113	256143F	30	1	160	72	2	1
114	749742D	43	1	155	70	2	1
115	123518F	46	1	156	45	1	2
116	366765D	31	1	165	70	1	2
117	71020F	46	1	150	44	2	2
118	208361F	46	1	151	61	2	1
119	772679D	71	1	155	55	2	1
120	65357D	50	1	149	65	1	2
121	220525F	46	1	150	61	2	2
122	242455F	40	1	150	44	1	2
123	235881F	54	1	150	45	2	3
124	903764D	41	1	150	48	2	1
125	169998F	66	1	160	58	2	3
126	337520A	30	1	160	68	2	1
127	186645F	46	1	151	77	2	1
128	203576F	35	1	148	64	1	1
129	86490F	33	1	140	60	1	3
130	216630F	62	1	150	44	2	2
131	238134F	59	1	150	50	2	2
132	206014D	50	1	160	59	2	1
133	777270D	43	1	160	68	1	1
134	185689F	73	1	150	46	2	2
135	223978F	50	1	150	49	1	2
136	70443B	67	1	150	45	2	1
137	306411F	45	1	157	75	2	2
138	303064F	56	1	160	64	1	3
139	539839C	50	1	150	75	2	1
140	878842A	41	1	152	79	2	1
141	210464F	61	1	155	48	1	2
142	255310F	49	1	151	70	2	1
143	243741F	71	1	144	48	2	1
144	595448C	49	1	155	64	1	1
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146	217753F	54	1	145	97	2	1
147	901444A	48	1	161	98	2	1
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149	301513F	40	1	157	56	1	2
150	591642B	66	1	140	65	2	2
151	325157D	46	1	158	70	1	1
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153	415821D	59	1	165	60	2	2
154	243484F	40	1	160	54	1	2
155	305932F	40	1	160	70	1	3

156	672531C	49	1	165	87	2	1	
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158	715254D	25	1	154	63	1	2	
159	368148A	66	1	159	64	2	3	
160	929291B	33	1	160	74	1	2	
161	254653F	49	1	151	65	1	1	
162	164694F	71	1	147	55	1	2	
163	453514B	29	1	168	59	1	2	
164	198288F	49	1	160	65	1	2	
165	300481F	52	1	150	70	2	3	
166	307233F	36	1	144	36	1	1	
167	273809F	45	1	165	47	1	2	
168	305093F	62	1	151	63	1	2	
169	187298F	69	1	165	54	1	2	
170	263568F	38	1	155	58	1	1	
171	983151D	47	1	161	80	1	1	
172	183960F	46	1	157	73	2	3	
173	175627B	43	1	150	79	2	2	
174	307095F	47	1	165	52	1	1	
175	316110F	29	1	160	56	1	2	
176	745292D	52	1	155	96	2	1	
177	162625C	60	1	157	42	2	3	
178	256214F	42	1	150	49	1	2	
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184	257584F	49	1	165	68	2	1	
185	187298F	69	1	155	54	2	2	
186	263568F	38	1	155	58	1	1	
187	564198B	37	1	165	78	1	2	
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189	116679F	53	1	150	43	1	1	
190	292547F	40	1	166	56	1	2	
191	926059C	26	1	159	47	1	2	
192	49088D	51	1	144	55	2	2	1
193	756769D	38	1	150	60	2	2	
194	285617F	47	1	150	46	2	3	
195	192068F	60	1	165	60	2	3	
196	271361F	49	1	162	61	2	1	
197	161683F	58	1	157	46	1	4	
198	700311A	55	1	165	45	1	2	
199	135972D	41	1	148	60	1	3	
200	292864F	42	1	147	64	2	2	

SURGERY	NO comor	Diabetes	HTN	Heart dise	CNS dis	obese	hypothyr	lung dis
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5	4	0	0	2	2	0	0	1
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5	3	5	5	0	0	0	0	0
3	1	0	0	2	2	0	0	2
3	2	0	0	3	6	0	0	0
4	2	0	0	2	2	0	0	0
4	4	3	5	0	6	0	0	3
3	2	0	0	5	5	0	0	2
2	2	0	0	2	2	0	0	3
4	3	0	0	2	2	0	0	0
4	4	9	5	0	0	0	0	2
2	2	5	5	0	0	0	0	0
3	2	9	9	0	0	0	0	2
2	2	9	5	0	0	0	0	0
2	3	0	0	2	3	0	0	1
4	2	3	3	0	3	0	0	0
2	2	4	4	0	6	0	0	3
2	3	0	0	2	2	0	0	0
5	2	3	3	0	6	0	0	3
4	5	0	0	2	2	0	0	0
4	4	7	7	0	6	0	0	0
3	4	3	5	0	6	0	0	1
4	2	0	0	2	2	0	0	2
3	1	0	0	2	2	0	0	2
3	2	0	0	2	2	0	0	1
1	6	3	5	0	0	0	0	0
3	4	0	0	2	2	0	0	0
5	2	3	3	0	0	0	0	1
2	2	5	5	0	0	0	0	2

3	2	3	5	0	0	0	0	0
3	1	0	0	2	2	0	0	2
4	3	0	0	2	3	0	0	0
2	2	5	0	0	0	0	0	0
3	2	3	3	0	6	0	0	1
3	3	0	0	2	2	0	0	1
4	4	3	3	0	0	0	0	2
2	3	0	0	0	3	0	0	3
2	2	9	5	0	0	0	0	2
3	2	5	0	0	0	0	0	1
3	4	10	5	0	0	0	0	1
3	2	9	9	0	0	0	0	2
3	5	9	9	0	0	0	0	0
3	4	3	3	0	6	0	0	1
4	3	3	5	0	6	0	0	0
3	2	9	9	0	0	0	0	2
3	3	0	5	0	0	0	0	1
2	3	0	0	2	3	0	0	0
2	2	3	5	0	0	0	0	0
4	2	0	0	3	0	0	0	0
3	2	9	9	0	0	0	0	2
3	3	0	0	0	0	0	0	2
5	4	3	5	0	6	0	0	1
2	3	3	3	0	6	0	0	0
4	2	0	0	3	3	0	0	0
1	1	5	0	0	0	0	0	1
3	2	0	0	3	3	0	0	2
3	2	0	0	2	2	0	0	2
4	4	0	0	2	3	0	0	1
3	4	3	3	0	6	0	0	1
4	4	3	5	0	6	0	0	0
2	2	0	0	0	0	0	0	0
1	1	0	0	0	3	0	0	1
4	2	0	0	2	2	0	0	1
4	3	0	0	2	2	0	0	3
2	2	0	0	2	2	0	0	0
3	3	0	0	2	2	0	0	0
6	3	5	0	0	0	0	0	2
4	2	0	0	0	0	0	0	2
1	1	0	0	0	0	0	0	1
3	4	3	5	0	0	0	0	3
4	2	0	0	3	3	0	0	1
3	2	0	0	2	2	0	0	1
6	4	0	0	3	0	0	0	1
4	4	0	0	3	3	0	0	1

D2 febrin	D1 aknil	D2 aknil	D1 perfal	D2 perfal	D1 metacir	D2 metacir	D1 ketonv	D2 ketonv
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3	0	0	0	0	0	0	0	0
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1	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	2	2	0	0	0	0
0	0	0	1	1	0	0	0	3
0	0	0	1	1	0	0	0	3
0	0	0	1	1	0	0	0	3
0	0	0	1	1	0	0	0	3
0	0	1	0	0	0	0	0	3
2	0	0	0	0	0	0	0	3
0	1	1	0	0	0	0	0	3
0	0	0	0	0	0	0	2	3
0	0	0	2	2	0	0	2	2
3	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
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2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	3	3
1	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	1	1
0	0	0	0	1	0	1	0	0
3	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
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2	0	0	0	0	0	0	3	3
1	0	0	0	0	1	1	3	3
2	0	0	0	0	0	2	0	0
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3	0	0	0	0	0	0	0	0
0	0	0	1	1	0	0	0	0
0	0	0	0	0	0	1	0	0
2	1	1	0	0	0	1	0	0
0	1	0	0	0	0	1	0	0
1	0	0	0	0	0	0	0	3
1	0	0	0	0	0	1	0	3
1	0	0	0	0	0	0	0	0
0	1	1	0	0	0	0	0	0
2	0	1	0	0	0	0	0	0
0	1	1	1	1	0	0	0	0

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0	0	0	2	2	0	1	0	0
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1	0	0	0	0	0	1	0	0
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1	0	0	0	0	0	1	0	0
0	0	0	2	2	0	1	0	3
0	0	0	1	1	0	0	0	0
0	0	0	1	1	0	1	0	0
0	0	0	1	1	0	1	0	0
0	0	0	0	0	0	1	0	0
0	0	0	2	2	0	0	0	3
2	1	1	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
2	1	1	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
0	1	1	0	0	0	1	1	3
1	0	0	0	0	0	0	0	0
1	0	1	0	0	0	0	0	1
2	0	1	0	0	0	0	0	2
0	1	1	0	0	0	1	0	0
0	1	1	0	0	0	1	1	3
0	0	0	1	1	0	0	0	0
1	1	1	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
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0	0	0	0	0	1	1	3	3
3	0	0	0	0	0	1	0	3
1	0	0	0	0	1	1	0	0
0	0	0	0	2	1	1	1	3
1	0	0	0	0	0	1	0	0
0	0	0	0	0	0	1	2	3
0	1	1	0	0	0	1	0	3
3	0	0	0	0	0	3	0	0
2	0	0	0	0	0	3	0	0
0	1	1	0	0	0	0	2	2
1	0	0	0	0	0	0	0	0
0	1	1	0	0	0	0	2	2
1	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	3
3	1	1	0	0	0	0	0	0
1	0	0	0	0	0	1	0	0
0	0	0	1	1	0	1	0	0
2	0	0	0	0	0	0	0	3

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2	0	0	0	2	0	0	0	3
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0	0	0	0	0	0	1	0	3
1	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	3
3	0	0	0	0	0	0	0	0
3	0	0	0	0	0	1	0	0
0	1	0	0	0	0	1	2	3
0	1	0	0	0	0	1	2	3
1	0	1	0	0	0	1	0	0
0	0	0	2	3	0	1	0	0
1	0	0	0	0	0	1	0	0
2	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
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1	0	1	0	0	0	1	0	0
2	0	0	0	0	0	0	0	3
0	0	1	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	1	1	0	0	0	0
0	0	0	0	0	0	1	0	0
3	0	0	0	0	0	0	0	0
0	0	0	0	0	0	1	0	0
0	1	1	0	0	0	0	0	0
2	0	0	0	0	0	3	0	0
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0	0	0	0	0	0	1	0	0
0	1	0	0	0	0	0	0	3
0	0	0	0	0	0	1	0	0
0	0	0	3	3	0	0	0	0
0	0	0	1	0	0	1	0	0
1	0	0	0	0	0	0	0	0
2	0	0	0	0	0	1	0	3
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	1	0	3
0	0	0	1	1	0	0	0	0
0	0	0	1	1	0	0	0	0
1	0	0	0	0	0	2	0	0
2	0	0	0	0	0	0	0	0

0	0	0	1	1	0	0	0	3
2	0	0	0	0	0	1	0	0
0	0	0	1	1	0	0	0	0
0	0	0	1	1	0	0	0	0
3	0	0	0	0	0	0	0	0
1	0	0	0	0	0	1	0	0
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2	0	0	0	0	0	1	0	0
0	0	0	2	2	0	0	0	0
3	0	0	0	0	0	1	0	0
0	0	0	0	0	0	1	0	0
2	0	0	0	0	0	3	0	0
1	0	0	0	0	0	0	0	0
0	1	1	0	0	0	0	0	0
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2	0	0	0	0	0	1	0	3
1	0	0	0	0	0	1	0	3
3	0	0	0	0	0	1	0	0
0	0	0	0	0	0	1	0	0
0	0	0	0	0	1	0	4	0
1	0	0	0	0	0	0	0	3
1	0	0	0	0	0	0	0	3
3	0	0	0	0	0	0	0	3
0	1	0	0	0	0	0	0	0
0	1	0	0	0	0	0	3	0
2	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
3	0	0	0	0	0	1	0	0
1	0	0	0	0	0	0	0	0
1	0	0	0	0	0	1	0	0
1	0	0	0	0	0	1	0	3
1	0	0	0	0	0	1	0	3

D1 voverar	D2 voverar	D1 proxy	D2 proxy	D1 emest	D2 emest	D1 phener	D2 phener	D1 rantac
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0	0	0	0	5	5	0	0	0
0	0	0	0	1	1	0	0	0
0	0	0	0	1	1	4	4	0
0	0	0	0	1	1	0	0	0
0	0	0	0	3	3	4	4	1
0	0	0	0	3	3	4	4	1
0	0	0	0	3	3	4	4	1
0	0	0	0	3	3	4	4	1
0	0	0	0	3	3	4	4	1
0	0	0	0	3	3	4	4	3
1	1	0	0	0	0	0	3	0
0	0	0	0	2	2	4	4	0
0	0	0	0	2	2	0	0	1
0	0	0	0	2	4	0	0	0
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0	0	0	2	3	4	4	4	4
0	0	1	1	3	3	4	4	2
0	0	1	1	0	4	0	0	0
1	1	0	0	1	1	0	0	0
0	0	0	0	1	4	4	4	0
0	0	0	0	0	0	0	0	0
0	1	0	0	0	4	0	0	0
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1	1	0	0	1	1	0	0	0
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0	0	0	0	2	2	4	4	1
0	0	1	1	1	1	4	4	1
0	0	0	1	2	4	5	5	1
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1	0	0	0	0	4	6	6	0
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0	0	0	0	2	2	4	4	1
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0	0	0	0	1	4	0	0	0
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0	0	0	0	1	1	0	0	0
1	1	0	0	1	1	0	0	0
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0	0	0	2	2	3	4	4	1
2	1	0	0	1	4	0	0	1
0	0	0	0	0	2	0	0	0
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0	1	0	0	1	1	3	3	0
1	1	0	0	1	3	0	0	0

0	0	0	0	2	2	6	6	0
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0	0	0	1	2	2	4	4	1
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0	0	0	1	1	1	4	4	1
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0	0	0	0	1	3	0	0	1
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1	1	0	0	1	3	0	0	0
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0	1	0	0	2	2	4	4	3
0	0	0	1	3	3	4	4	1
0	0	0	0	2	2	3	3	1
1	1	0	0	1	3	0	0	0
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1	1	0	0	1	1	0	0	0
0	1	0	0	2	2	1	1	0
0	0	0	0	1	1	0	0	0
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0	0	1	1	1	1	3	3	1
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0	1	0	0	1	4	0	0	1
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0	0	0	0	2	3	4	3	1
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0	0	0	0	3	0	4	4	0
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0	0	0	0	1	4	0	0	0
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0	0	0	1	2	4	4	4	1
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0	0	0	0	0	3	0	0	0
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0	0	0	0	2	2	4	4	3
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0	0	0	2	3	0	4	4	1
3	3	0	0	0	0	4	4	0
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0	0	0	0	1	1	0	0	0
0	0	0	1	2	4	4	4	1
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0	0	0	0	2	6	4	4	0
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